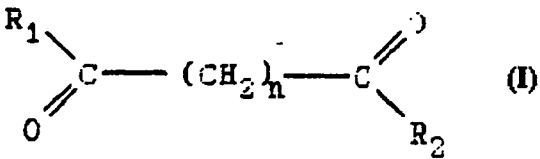




## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

<b>(51) International Patent Classification <sup>6</sup> :</b> <b>A61K 31/16, 31/195, 31/22, 31/235, C07C 233/16, 233/17, 233/22, 233/30, 233/31, 233/33, 233/46, 233/51, 233/53, 237/20, 237/24, 237/28</b>	<b>A1</b>	<b>(11) International Publication Number:</b> <b>WO 95/31977</b> <b>(43) International Publication Date:</b> 30 November 1995 (30.11.95)
<b>(21) International Application Number:</b> PCT/US95/06554 <b>(22) International Filing Date:</b> 19 May 1995 (19.05.95)  <b>(30) Priority Data:</b> 08/246,363      19 May 1994 (19.05.94)      US  <b>(71) Applicants:</b> SLOAN-KETTERING INSTITUTE FOR CANCER RESEARCH [US/US]; 1275 York Avenue, New York, NY 10021 (US). THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK [US/US]; West 116th Street & Broadway, New York, NY 10027 (US).  <b>(72) Inventors:</b> BRESLOW, Ronald; 275 Broad Avenue, Englewood, NJ 07631 (US). MARKS, Paul, A.; 7 Rossiter Road, Washington, CT 06793 (US). RIFKIND, Richard, A.; 30 Sutton Place, New York, NY 10022 (US).  <b>(74) Agent:</b> WHITE, John, P.; Cooper & Dunham LLP, 1185 Avenue of the Americas, New York, NY 10036 (US).		<b>(81) Designated States:</b> AU, CA, JP, MX, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).  <b>Published</b> <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> NOVEL POTENT INDUCERS OF TERMINAL DIFFERENTIATION AND METHODS OF USE THEREOF  <b>(57) Abstract</b> <p>The present invention provides the compound having structure (I), wherein each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other; when R<sub>1</sub> and R<sub>2</sub> are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiazoleamino group; when R<sub>1</sub> and R<sub>2</sub> are different, R<sub>1</sub> = R<sub>3</sub>-N-R<sub>4</sub>, wherein each of R<sub>3</sub> and R<sub>4</sub> are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or R<sub>3</sub> and R<sub>4</sub> bond together to form a piperidine group and R<sub>2</sub> is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and n is an integer from about 4 to about 8. The present invention also provides a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells. Moreover, the present invention provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells. Lastly, the present invention provides a pharmaceutical composition comprising a pharmaceutically acceptable carrier and a therapeutically acceptable amount of the compound above.</p> <div style="text-align: center; margin-top: 20px;">  <p style="text-align: right;">(I)</p> </div>		

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**NOVEL POTENT INDUCERS OF TERMINAL  
DIFFERENTIATION AND METHODS OF USE THEREOF**

This application is a continuation-in-part of U.S. Serial  
5 No. 07/771,760, filed October 4, 1991, the contents of  
which are hereby incorporated by reference in this  
disclosure. The invention described herein was made in  
the course of work under Grant Number CA-57227-01 from  
the National Institutes of Health. The United States  
10 Government has certain rights in this invention.

**Background of the Invention**

Throughout this application various publications are  
15 referenced by arabic numerals within parentheses. Full  
citations for these publications may be found at the end  
of the specification immediately preceding the claims.  
The disclosures of these publications in their entireties  
are hereby incorporated by reference into this  
20 application in order to more fully describe the state of  
the art to which this invention pertains.

Cancer is a disorder in which a population of cells has  
become, in varying degrees, unresponsive to the control  
25 mechanisms which normally govern proliferation and  
differentiation. For many years there have been two  
principal strategies for chemotherapeutic treatment of  
cancer: a) blocking hormone-dependent tumor cell  
proliferation by interference with the production or  
30 peripheral action of sex hormones; and b) killing cancer  
cells directly by exposing them to cytotoxic substances,  
which injure both neoplastic and normal cell populations.

35 Relatively recently, cancer therapy is also being  
attempted by the induction of terminal differentiation of  
the neoplastic cells (1). In cell culture models  
differentiation has been reported by exposure of cells to

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a variety of stimuli, including: cyclic AMP and retinoic acid (2,3), aclarubicin and other anthracyclines (4).

5 There is abundant evidence that neoplastic transformation does not necessarily destroy the potential of cancer cells to differentiate (1,5,6). There are many examples of tumor cells which do not respond to the normal regulators of proliferation and appear to be blocked in the expression of their differentiation program, and yet  
10 can be induced to differentiate and cease replicating. A variety of agents, including some relatively simple polar compounds (5,7-9), derivatives of vitamin D and retinoic acid (10-12), steroid hormones (13), growth factors (6,14), proteases (15,16), tumor promoters  
15 (17,18), and inhibitors of DNA or RNA synthesis (4,19-24), can induce various transformed cell lines and primary human tumor explants to express more differentiated characteristics.

20 Early studies by the present inventors identified a series of polar compounds that were effective inducers of differentiation in a number of transformed cell lines (8,9). Of these, the most effective inducer, was the hybrid polar/apolar compound N,N'-hexamethylene  
25 bisacetamide (HMBA) (9). The use of this polar/apolar compound to induce murine erythroleukemia cells (MELC) to undergo erythroid differentiation with suppression of oncogenicity has proved a useful model to study inducer-mediated differentiation of transformed cells (5,7-9).  
30 HMBA-induced MELC terminal erythroid differentiation is a multistep process. Upon addition of HMBA to MELC (745A-DS19) in culture, there is a latent period of 10 to 12 hours before commitment to terminal differentiation is detected. Commitment is defined as the capacity of cells  
35 to express terminal differentiation despite removal of inducer (25). Upon continued exposure to HMBA there is progressive recruitment of cells to differentiate. The

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present inventors have reported that MELC cell lines made resistant to relatively low levels of vincristine become markedly more sensitive to the inducing action of HMBA and can be induced to differentiate with little or no latent period (26).

HMBA is capable of inducing phenotypic changes consistent with differentiation in a broad variety of cells lines (5). The characteristics of the drug induced effect have been most extensively studied in the murine erythroleukemia cell system (MELC) (5,25,27,28). MELC induction of differentiation is both time and concentration dependent. The minimum concentration required to demonstrate an effect in vitro in most strains is 2 to 3 mM; the minimum duration of continuous exposure generally required to induce differentiation in a substantial portion (>20%) of the population without continuing drug exposure is about 36 hours.

The primary target of action of HMBA is not known. There is evidence that protein kinase C is involved in the pathway of inducer-mediated differentiation (29). The in vitro studies provided a basis for evaluating the potential of HMBA as a cytodifferentiation agent in the treatment of human cancers (30). Several phase I clinical trials with HMBA have been completed (31-36). Clinical trials have shown that this compound can induce a therapeutic response in patients with cancer (35,36). However, these phase I clinical trials also have demonstrated that the potential efficacy of HMBA is limited, in part, by dose-related toxicity which prevents achieving optimal blood levels and by the need for intravenous administration of large quantities of the agent, over prolonged periods.

Recently, the present inventors have reported a number of compounds related to HMBA with polar groups separated by

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apolar linkages that, on a molar basis, are as active (37) or 100 times more active than HMBA (38). As a class, however, it has been found that the symmetrical dimers such as HMBA and related compounds are not the  
5 best cytodifferentiating agents.

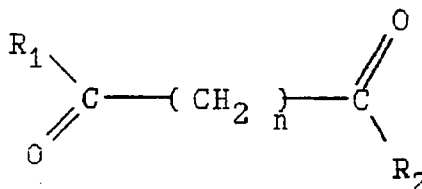
It has unexpectedly been found that the best compounds comprise two polar end groups separated by a flexible chain of methylene groups, wherein one or both of the  
10 polar end groups is a large hydrophobic group. Preferably, the polar end groups are different and only one is a large hydrophobic group. These compounds are unexpectedly a thousand times more active than HMBA and ten times more active than HMBA related compounds.

15 This new class of compounds of the present invention may be useful for selectively inducing terminal differentiation of neoplastic cells and therefore aid in treatment of tumors in patients.

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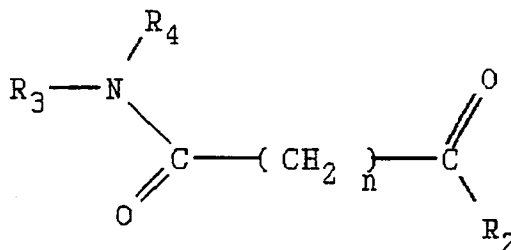
Summary of the Invention

The present invention provides the compound having the structure:



herein each of  $\text{R}_1$  and  $\text{R}_2$  are independently the same as or different from each other; when  $\text{R}_1$  and  $\text{R}_2$  are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiazoleamino group; when  $\text{R}_1$  and  $\text{R}_2$  are different,  $\text{R}_1 = \text{R}_3\text{-N-R}_4$ , wherein each of  $\text{R}_3$  and  $\text{R}_4$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or  $\text{R}_3$  and  $\text{R}_4$  bond together to form a piperidine group and  $\text{R}_2$  is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and  $n$  is an integer from about 4 to about 8.

The present invention also provides the compound above having the structure:

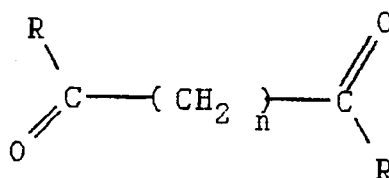


wherein each of  $\text{R}_3$  and  $\text{R}_4$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched

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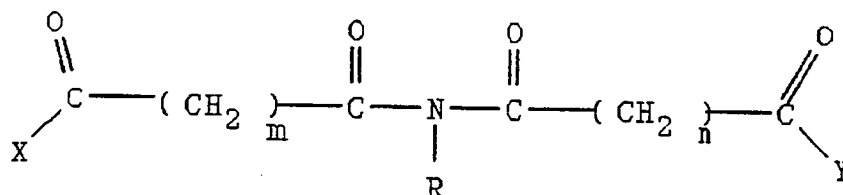
or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or  $R_3$  and  $R_4$  bond together to form a piperidine group;  $R_2$  is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and  $n$  is an integer from about 4 to about 8.

The present invention also provides the compound above having the structure:



wherein  $R$  is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiazoleamino group; and  $n$  is an integer from about 4 to about 8.

The present invention also provides the compound having the structure:



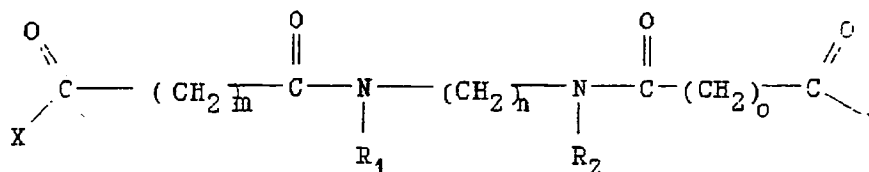
wherein each of  $X$  and  $Y$  are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group;  $R$  is a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of  $m$  and  $n$  are independently the same as or



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different from each other and are each an integer from about 0 to about 8.

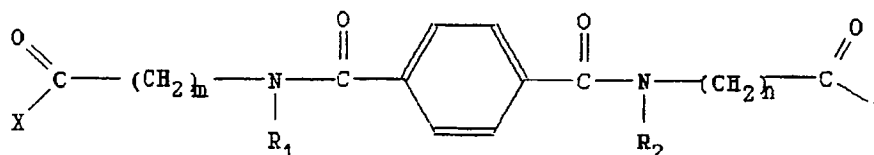
The present invention further provides the compound  
5 having the structure:



10

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m, n, and o are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention still further provides the compound  
25 having the structure:



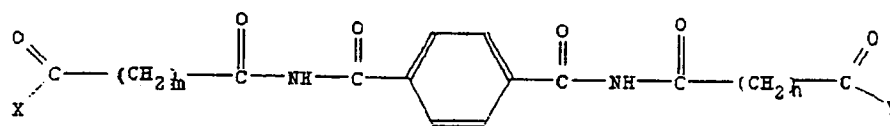
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wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino,

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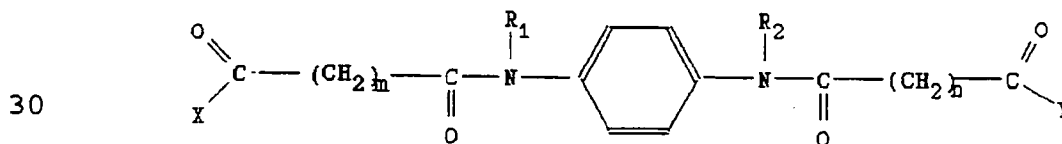
alkyloxyalkylamino, or aryloxyalkylamino group; each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of  $m$  and  $n$  are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention also provides the compound having the structure:



wherein each of  $X$  and  $Y$  are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and each of  $m$  and  $n$  are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention also provides the compound having the structure:

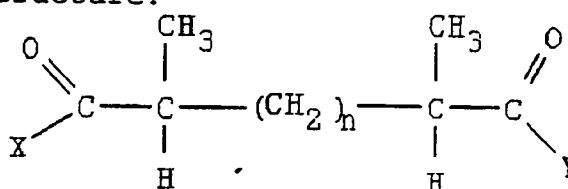


wherein each of  $X$  and  $Y$  are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino,

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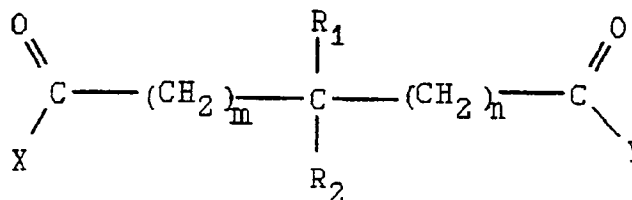
alkyloxyalkylamino, or aryloxyalkylamino group; each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of  $m$  and  $n$  are independently the same as or different from each other and are each an integer from about 0 to about 8.

The present invention further provides the compound having the structure:



wherein each of  $X$  and  $Y$  are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and  $n$  is an integer from about 0 to about 8.

The present invention still further provides the compound having the structure:

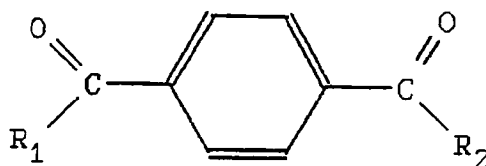


wherein each of  $X$  and  $Y$  are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of

-10-

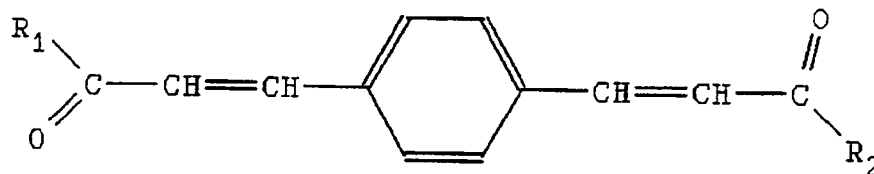
$R_1$  and  $R_2$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, aryloxy, carbonylhydroxylamino, or fluoro group; and  
5 each of  $m$  and  $n$  are independently the same as or different from each other and are each an integer from about 0 to about 8.

10 The present invention also provides the compound having the structure:



wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino,  
20 arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

The present invention also provides the compound having the structure:

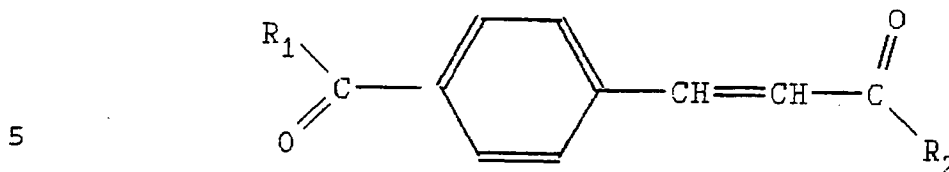


30 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino,  
35 alkyloxyalkylamino, or aryloxyalkylamino group.

The present invention further provides the compound

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having the structure:

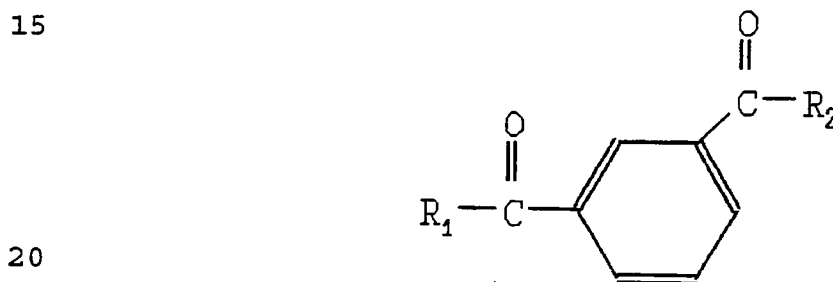


wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

10

The present invention further provides the compound having the structure:

15

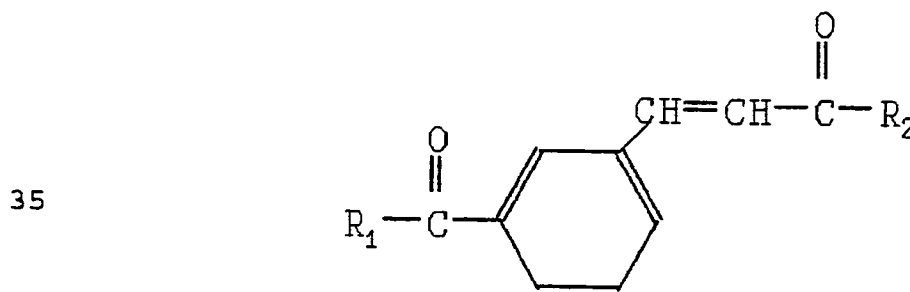


wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

25

The present invention further provides the compound having the structure:

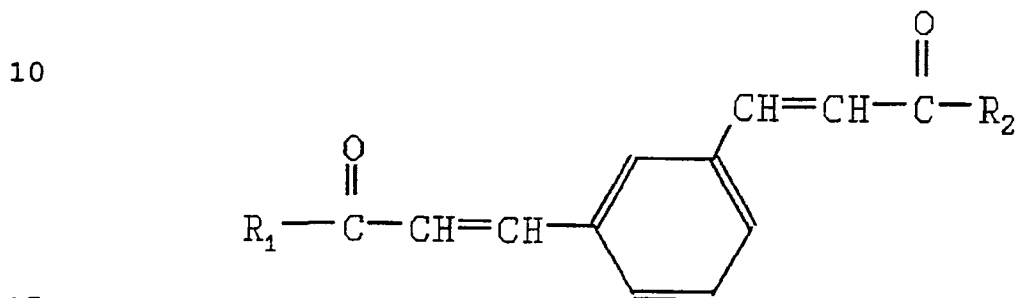
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wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, 5 alkyloxyalkylamino, or aryloxyalkylamino group.

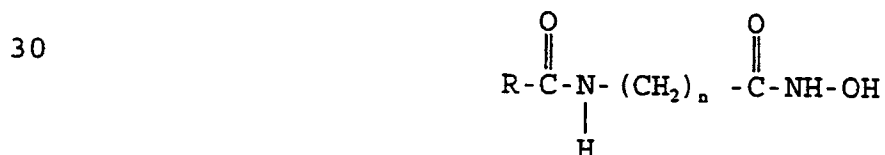
The present invention further provides the compound having the structure:



wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, 20 arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

The present invention also provides the pharmaceutically acceptable salts of any of the compounds defined above.

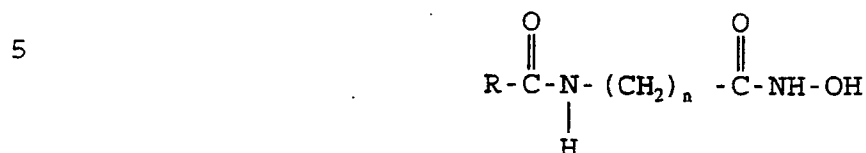
25 The present invention further provides a compound having the structure:



wherein  $R$  is a substituted or unsubstituted phenyl, piperidine or thiazole group and  $n$  is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

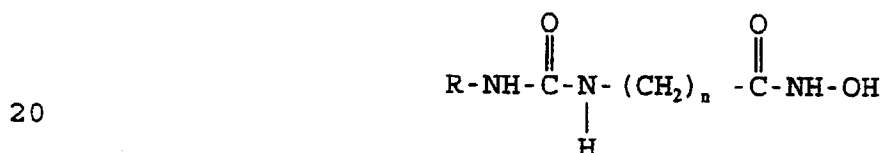
-13-

The present invention also provides a compound having the structure:



10 wherein R is a substituted or unsubstituted 2-pyridine, 3-pyridine, or 4-pyridine and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

15 The present invention further provides a compound having the structure:



25 wherein R is a substituted or unsubstituted phenyl, pyridine, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

30 In addition, the present invention provides a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells which comprises contacting the cells under suitable conditions with an effective amount of any of the compounds above, effective to selectively induce terminal differentiation.

35 The present invention also provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells which comprises administering to the patient an effective amount of any of the compounds  
40 above, effective to selectively induce terminal differentiation of such neoplastic cells and thereby inhibit their proliferation.

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The present invention also provides a pharmaceutical composition comprising a therapeutically acceptable amount of any of the compounds above, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier.

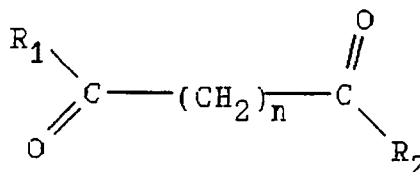
Lastly, the present invention provides the pharmaceutical composition defined above, alone or in combination with an antitumor agent, in sustained release form.



Detailed Description of the Invention

The present invention provides the compound having the structure:

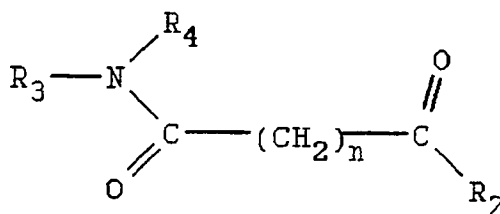
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- 10 wherein each of  $\text{R}_1$  and  $\text{R}_2$  are independently the same as or different from each other; when  $\text{R}_1$  and  $\text{R}_2$  are the same, each is a substituted or unsubstituted arylamino, cycloalkyl-amino, pyridineamino, piperidino, 9-purine-6-amine, or thiazoleamino group; when  $\text{R}_1$  and  $\text{R}_2$  are
- 15 different,  $\text{R}_1 = \text{R}_3\text{-N-R}_4$ , wherein each of  $\text{R}_3$  and  $\text{R}_4$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or
- 20 pyridino group, or  $\text{R}_3$  and  $\text{R}_4$  bond together to form a piperidine group and  $\text{R}_2$  is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and  $n$  is an integer from about 4 to about 8.

- 25 The present invention also provides the compound above having the structure:

30



- wherein each of  $\text{R}_3$  and  $\text{R}_4$  are independently the same as or different from each other and are a hydrogen atom, a
- 35 hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or  $\text{R}_3$  and  $\text{R}_4$

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bond together to form a piperidine group;  $R_2$  is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and  $n$  is an integer from about 4 to about 8.

5

In the preferred embodiment of the compound above,  $R_2$  is a hydroxylamino, hydroxyl, amino, methylamino, dimethylamino, or methoxy group and  $n$  is 6. Most preferably,  $R_4$  is a hydrogen atom and  $R_3$  is a substituted or unsubstituted phenyl group.

10

The phenyl group may be substituted with a methyl, cyano, nitro, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, benzyloxy, phenylaminooxy, phenylmethoxy, phenylamino-carbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylamino-carbonyl group.

15

20

In other preferred embodiments of the compound above,  $R_4$  is a hydrogen atom and  $R_3$  is a cyclohexyl group;  $R_4$  is a hydrogen atom and  $R_3$  is a methoxy group;  $R_3$  and  $R_4$  each bond together to form a piperidine group;  $R_4$  is a hydrogen atom and  $R_3$  is a hydroxyl group;  $R_4$  is a hydrogen atom and  $R_3$  is a benzyloxy group;  $R_4$  is a hydrogen atom and  $R_3$  is a  $\delta$ -pyridine group;  $R_4$  is a hydrogen atom and  $R_3$  is a  $\beta$ -pyridine group;  $R_4$  is a hydrogen atom and  $R_3$  is a  $\alpha$ -pyridine group;  $R_3$  and  $R_4$  are both methyl groups; or  $R_4$  is a methyl group and  $R_3$  is a phenyl group.

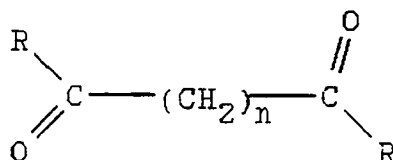
25

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- 17 -

The present invention also provides the compound having the structure:

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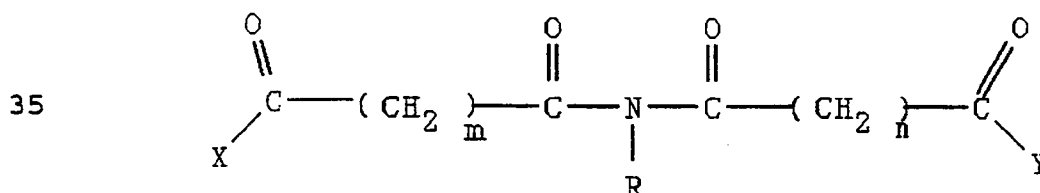
10 wherein R is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiazoleamino group; and n is an integer from about 4 to about 8.

15 In the preferred embodiment of the compound above, R is  
a substituted or unsubstituted phenylamino group. The  
phenylamino group may be substituted with a cyano,  
methylcyano, nitro, carboxyl, aminocarbonyl,  
methyldaminocarbonyl, dimethyldaminocarbonyl,  
20 trifluoromethyl, hydroxyldaminocarbonyl, N-  
hydroxyldaminocarbonyl, methoxycarbonyl, chloro, fluoro,  
methyl, methoxy, 2,3-difluoro, 2,3-difluoro, 2,4-  
difluoro, 2,5-difluoro, 2,6-difluoro, 3,5-difluoro, 2,6-  
difluoro, 2,3,6-trifluoro, 1,2,3-trifluoro, 3,4,5-  
25 trifluoro, 2,3,4,5-tetrafluoro, or 2,3,4,5,6-pentafluoro  
group.

In another embodiment of the compound above, R is a cyclohexylamino group.

30

The present invention also provides the compound having the structure:

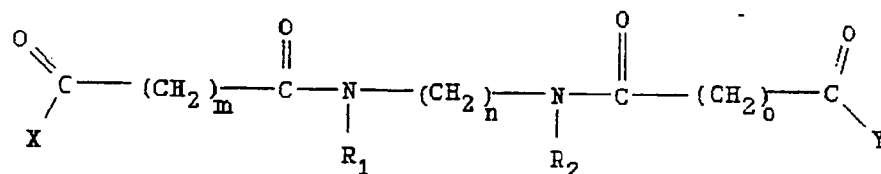


-18-

wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; R is a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In the preferred embodiment of the compound above, each of X, Y, and R is a hydroxyl group and each of m and n is 5.

The present invention also provides the compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m, n, and o are independently the same as or different from each other and are each an integer from about 0 to about 8.

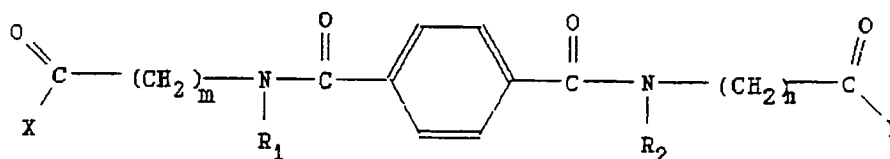
-19-

In the preferred embodiment of the compound above, each of X and Y is a hydroxyl group and each of R<sub>1</sub> and R<sub>2</sub> is a methyl group. Most preferably, each of n and o is 6, and m is 2.

5

The present invention also provides the compound having the structure:

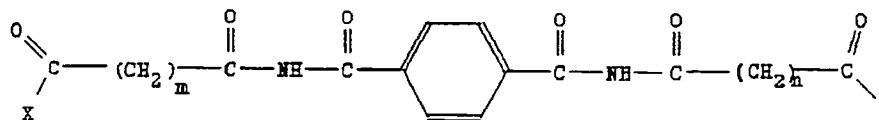
10



15 wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, 20 alkyloxyalkylamino, or aryloxyalkylamino group; each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the 25 same as or different from each other and are each an integer from about 0 to about 8.

The present invention also provides the compound having the structure:

30



35

wherein each of X and Y are independently the same as or

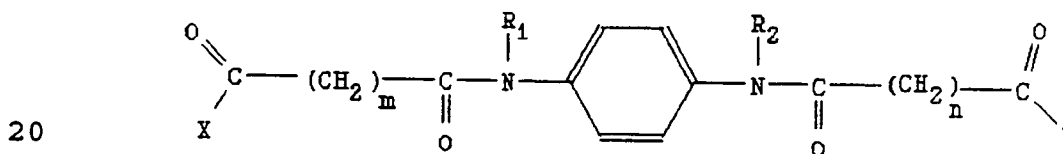
-20-

different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

In the preferred embodiment of the compound above, each of X and Y is a hydroxyl group and each of m and n is 5.

The present invention also provides the compound having the structure:

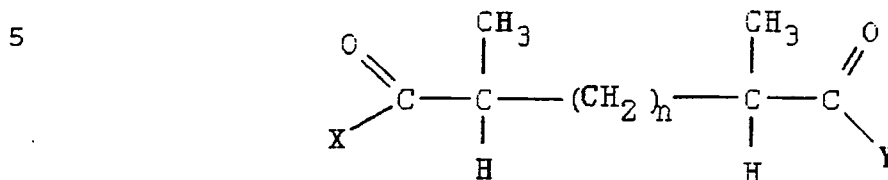
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wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

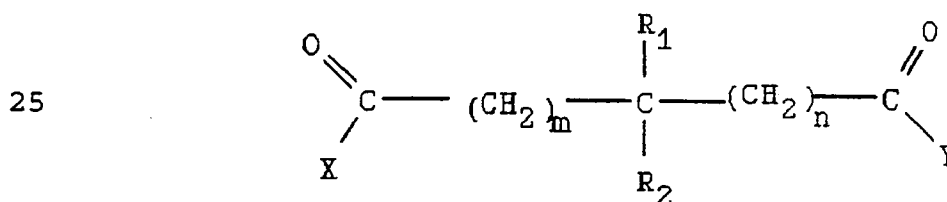
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The present invention also provides the compound having the structure:



10 wherein each of X and Y are independently the same as or  
different from each other and are a hydroxyl, amino or  
hydroxylamino group, a substituted or unsubstituted  
alkyloxy, alkylamino, dialkylamino, arylamino,  
alkylarylamino, alkyloxyamino, aryloxyamino,  
15 alkyloxyalkylamino, or aryloxyalkylamino group; and n is  
an integer from about 0 to about 8.

In the preferred embodiment of the compound above, each of X and Y is a dimethylamino group and n is 4 or 5.



wherein each of X and Y are independently the same as or  
30 different from each other and are a hydroxyl, amino or  
hydroxylamino group, a substituted or unsubstituted  
alkyloxy, alkylamino, dialkylamino, arylamino,  
alkylaryl amino, alkyloxyamino, aryloxyamino,  
alkyloxyalkylamino, or aryloxyalkylamino group; each of  
35 R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from  
each other and are a hydrogen atom, a hydroxyl group, a  
substituted or unsubstituted alkyl, aryl, alkyloxy,

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aryloxy, carbonylhydroxylamino, or fluoro group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8.

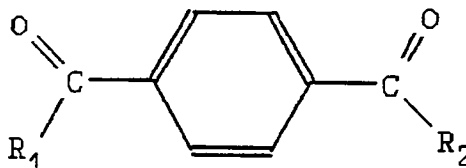
5

In the preferred embodiment of the compound above, each of X and Y is a hydroxylamino group, R<sub>1</sub> is a methyl group, R<sub>2</sub> is a hydrogen atom, and each of m and n is 2. In another preferred embodiment, each of X and Y is a hydroxylamino group, R<sub>1</sub> is a carbonylhydroxylamino group, R<sub>2</sub> is a hydrogen atom, and each of m and n is 5. In a further preferred embodiment, each of X and Y is a hydroxylamino group, each of R<sub>1</sub> and R<sub>2</sub> is a fluoro group, and each of m and n is 2.

15

The present invention also provides the compound having the structure:

20



25 wherein each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamine, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

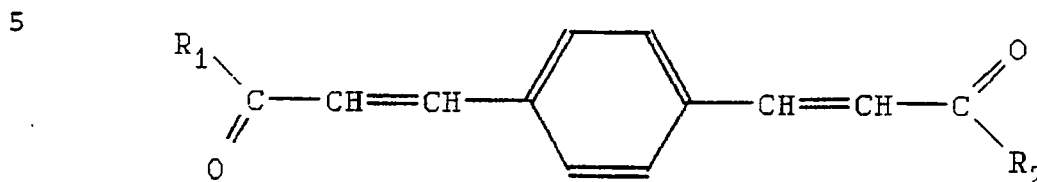
30

Preferably, R<sub>1</sub> is a phenylamino group and R<sub>2</sub> is a hydroxylamino group.



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The present invention also provides the compound having the structure:

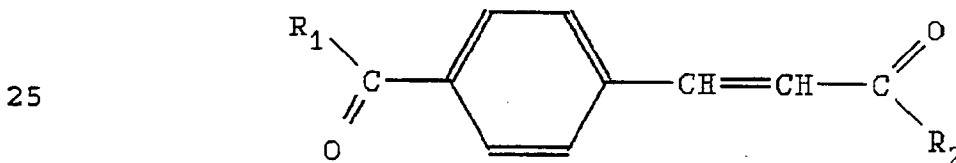


10 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

15

Preferably,  $R_1$  is phenylamino group and  $R_2$  is hydroxylamino group.

20 The present invention also provides the compound having the structure:

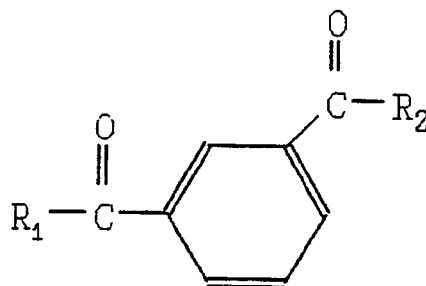


30 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

35 In the preferred embodiment, either  $R_1$  or  $R_2$  is a hydroxylamino group.

The present invention also provides the compound having

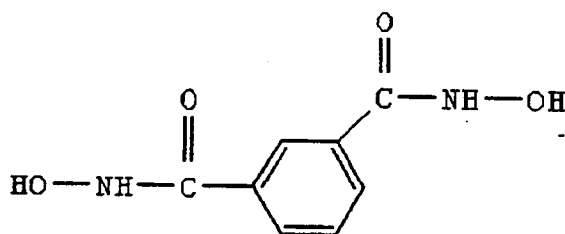
the structure:



10 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

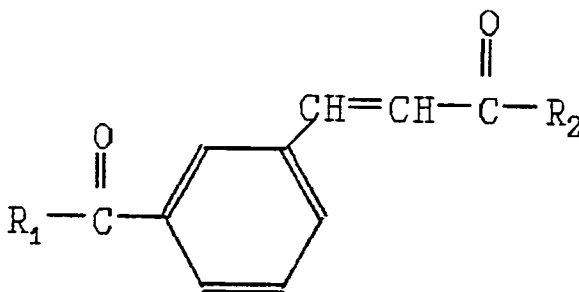
15

In a preferred embodiment, the compound above has the structure:



25

The present invention also provides a compound having the structure:

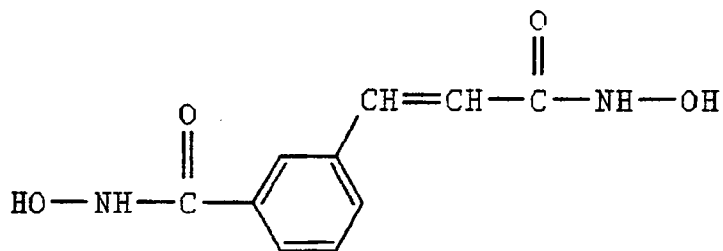


-25-

wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

In a preferred embodiment, the compound above has the structure:

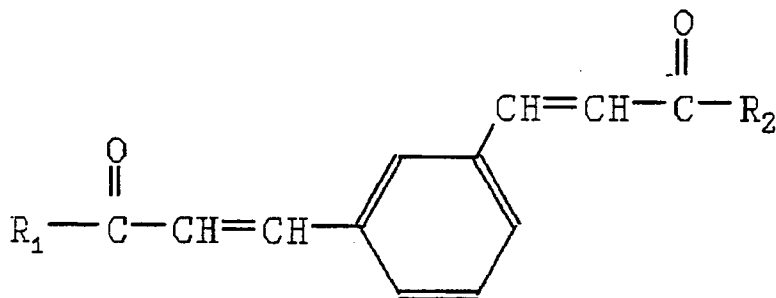
10



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The present invention also provides a compound having the structure:

20

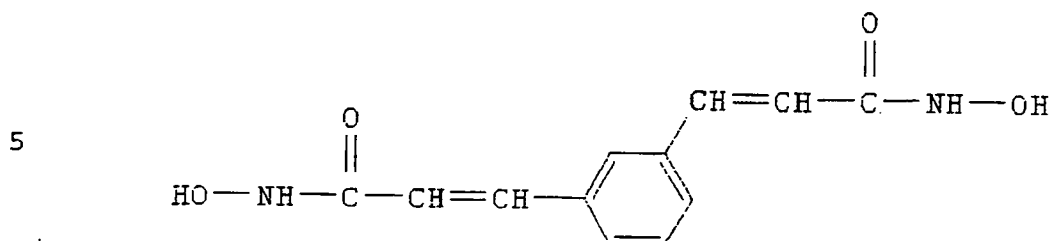


25

wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group.

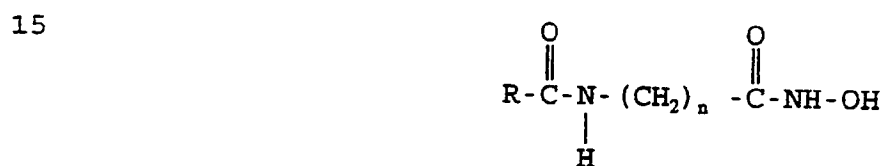
In the preferred embodiment, the compound defined above has the structure:

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10 The present invention also provides the pharmaceutically acceptable salts of any of the compounds defined above.

The present invention further provides a compound having the structure:



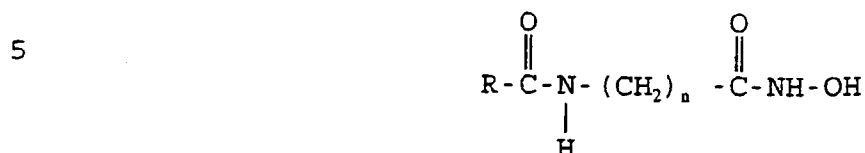
25 wherein R is a substituted or unsubstituted phenyl, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

30 In a preferred embodiment of the compound defined above R is a substituted phenyl group. In a more preferred embodiment the phenyl group is substituted with a methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylamino-carbonyl, or hydroxylaminocarbonyl group.

35

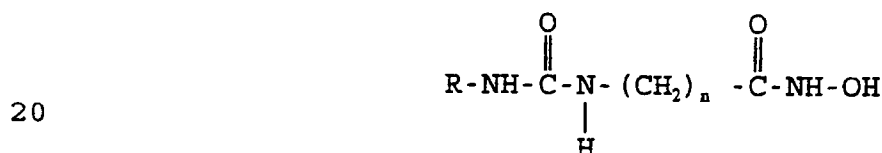
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The present invention also provides a compound having the structure:



10 wherein R is a substituted or unsubstituted 2-pyridine, 3-pyridine, or 4-pyridine and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

15 The present invention further provides a compound having the structure:



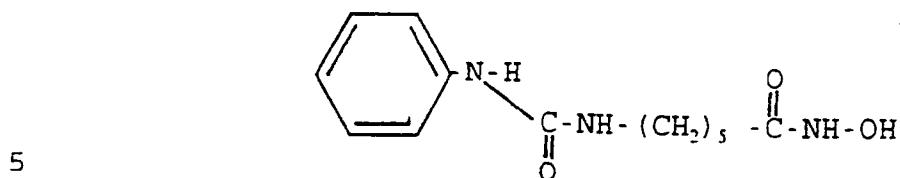
25 wherein R is a substituted or unsubstituted phenyl, pyridine, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the compound defined above, R is a substituted phenyl group. In a more preferred  
30 embodiment, the phenyl group is substituted with a methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-  
35 trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminoxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino,  
40 dimethylamino-carbonyl, or hydroxylaminocarbonyl group.

In a further preferred embodiment the compound defined

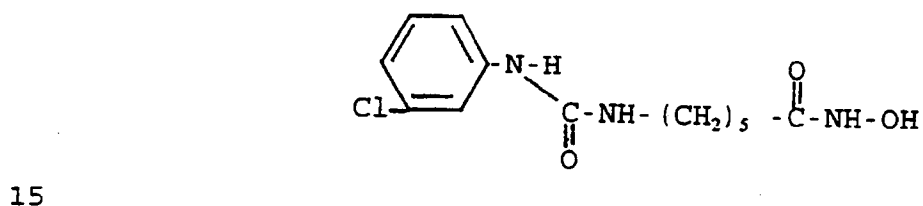
- 28 -

above has the structure:



or a pharmaceutically acceptable salt thereof.

10 In a further preferred embodiment the compound defined above has the structure:



or a pharmaceutically acceptable salt thereof.

20 The present invention further provides a method of selectively inducing terminal differentiation of neoplastic cells and thereby inhibiting proliferation of such cells which comprises contacting the cells under suitable conditions with an effective amount of any of the compounds above, effective to selectively induce terminal differentiation.

25 The contacting must be performed continuously for a prolonged period of time, i.e. for at least 48 hours, preferably for about 4-5 days or longer.

30 The method may be practiced in vivo or in vitro. If the method is practiced in vitro, contacting may be effected by incubating the cells with the compound. The concentration of the compound in contact with the cells should be from about 1  $\mu$ M to about 25 mM, preferably from 35 4  $\mu$ M to about 5 mM. The concentration depends upon the individual compound and the state of the neoplastic cells.

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The method may also comprise initially treating the cells with an antitumor agent so as to render them resistant to an antitumor agent and subsequently contacting the resulting resistant cells under suitable conditions with an effective amount of any of the compounds above, effective to selectively induce terminal differentiation of such cells.

The antitumor agent may be one of numerous chemotherapy agents such as an alkylating agent, an antimetabolite, a hormonal agent, an antibiotic, colchicine, a vinca alkaloid, L-asparaginase, procarbazine, hydroxyurea, mitotane, nitrosoureas or an imidazole carboxamide. Suitable agents are those agents which promote depolarization of tubulin. Preferably the antitumor agent is colchicine or a vinca alkaloid; especially preferred are vinblastine and vincristine. In embodiments where the antitumor agent is vincristine, the cells preferably are treated so that they are resistant to vincristine at a concentration of about 5 mg/ml. The treating of the cells to render them resistant to an antitumor agent may be effected by contacting the cells with the agent for a period of at least 3-5 days. The contacting of the resulting cells with any of the compounds above is performed as described previously.

The present invention also provides a method of treating a patient having a tumor characterized by proliferation of neoplastic cells which comprises administering to the patient an effective amount of any of the compounds above, or pharmaceutically acceptable salts thereof, effective to selectively induce terminal differentiation of such neoplastic cells and thereby inhibit their proliferation.

The method of the present invention is intended for the treatment of human patients with tumors. However, it is

-30-

also likely that the method would be effective in the treatment of tumors in other mammals. The term tumor is intended to include any cancer caused by the proliferation of neoplastic cells, such as lung cancer, acute lymphoid myeloma, bladder melanoma, renal carcinoma, breast carcinoma, or colorectal carcinoma. The administration of the compound to the patient may be effected orally or parenterally. To date, administration intravenously has proven to be effective. The administration of the compound must be performed continuously for a prolonged period of time, such as for at least 3 days and preferably more than 5 days. In the most preferred embodiments, the administration is effected continuously for at least 10 days and is repeated at intervals wherein at each interval the administration is continuously effected for at least 10 days. For example, the administration may be effected at intervals as short as 5-10 days, up to about 25-35 days and continuously for at least 10 days during each such interval. The optimal interval period will vary depending on the type of patient and tumor. For example, in the incidence of acute leukemia, the so called myelodysplastic syndrome, continuous infusion would seem to be indicated so long as the patient tolerated the drug without toxicity and there was a positive response.

The amount of the compound administered to the patient is less than an amount which would cause toxicity in the patient. In the certain embodiments, the amount of the compound which is administered to the patient is less than the amount which causes a concentration of the compound in the patient's plasma to equal or exceed the toxic level of the compound. Preferably, the concentration of the compound in the patient's plasma is maintained at about 1.0 mM. It has been found with HMBA that administration of the compound in an amount from about 5 gm/m<sup>2</sup>/day to about 30 gm/m<sup>2</sup>/day, particularly



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about 20 gm/m<sup>2</sup>/day, is effective without producing toxicity in the patient. The optimal amount of the compound which should be administered to the patient in the practice of the present invention will depend on the particular compound used and the type of cancer being treated.

This invention, in addition to the above listed compounds, is intended to encompass the use of homologs and analogs of such compounds. In this context, homologs are molecules having substantial structural similarities to the above-described compounds and analogs are molecules having substantial biological similarities regardless of structural similarities.

The method may also comprise initially administering to the patient an amount of an antitumor agent to render the cells resistant to an antitumor agent and subsequently administering to the patient an effective amount of any of the compounds above, or pharmaceutically acceptable salts thereof, effective to selectively induce terminal differentiation of such neoplastic cells and thereby inhibit their proliferation.

The antitumor agent may be one of numerous chemotherapy agents such as an alkylating agent, an antimetabolite, a hormonal agent, an antibiotic, colchicine, a vinca alkaloid, L-asparaginase, procarbazine, hydroxyurea, mitotane, nitrosoureas or an imidazole carboxamide. Suitable agents are those agents which promote depolarization of tubulin. Preferably the antitumor agent is colchicine or a vinca alkaloid; especially preferred are vinblastine and vincristine. In embodiments where the antitumor agent is vincristine, an amount is administered to render the cells are resistant to vincristine at a concentration of about 5 mg/ml. The administration of the agent is performed essentially as

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described above for the administration of any of the compounds. Preferably, the administration of the agent is for a period of at least 3-5 days. The administration of any of the compounds above is performed as described previously.

The present invention also provides a pharmaceutical composition comprising a therapeutically acceptable amount of any of the compounds above, or pharmaceutically acceptable salts thereof, and a pharmaceutically acceptable carrier, such as sterile pyrogen-free water. Preferably, the therapeutically acceptable amount is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.

The present invention provides the pharmaceutical composition above in combination with an antitumor agent. The antitumor agent may be any of the agents previously described.

Lastly, the present invention provides the pharmaceutical composition above, alone or in combination with an antitumor agent, in sustained release form. By "sustained release form" applicants mean incorporation of the pharmaceutical compositions in a pharmaceutically acceptable formulation which provides for the sustained release of a therapeutically effective amount of the compounds of this invention over a period of time necessary to derive the intended therapeutic effect. Sustained release formulations of pharmaceutical compositions allow for less frequent administration of the compound and provide for administration of the pharmaceutical composition at or near the target area in a subject's system. Sustained release formulations and methods of incorporating pharmaceutical compositions therein are well known to those of ordinary skill in the

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art. Examples include, but are not limited to, such formulations as incorporation into ion exchange resins (U.S. Patent No. 5,296,228 to Chang et al.), xanthan gums (U.S. Patent No. 5,292,534 to Valentine et al.),  
5 microspheres (U.S. Patent No. 5,288,502 to McGinity et al.) hydrogels (U.S. Patent No. 5,266,325 to Kuzma et al.) and solid forms such as wax-like or fat-like hydrophobic substances containing water insoluble polymers (U.S. Patent No. 5,270,055 to Moest). Methods  
10 of administering compounds for sustained release are also known in the art and include, but are not limited to, surgical implantation of microencapsulated pharmaceutical compounds near the intended target site (U.S. Patent No. 5,290,271 to Jernberg) and incorporation of compound into  
15 transdermal patches (U.S. Patent No. 5,298,256 to Flockhart et al. and U.S. Patent No. 5,290,561 to Farhadieh et al.). The text of the above cited patents and the references disclosed therein are hereby incorporated by reference in their entirety into this  
20 disclosure.

The invention is illustrated in the Experimental Details section which follows. This section is set forth to aid in an understanding of the invention but is not intended  
25 to, and should not be construed to, limit in any way the invention as set forth in the claims which follow thereafter.

Experimental DetailsCells and Materials

5 MELC 745A-DS19 cells and the variants of MELC derived  
from this cell line, namely, the vincristine-resistant  
MELC V3.17 and VCR.C(2)15 cell lines (26), and the  
dimethylsulfoxide-resistant cell line, DR10 (39), were  
10 maintained in alpha minimal essential medium containing  
10% fetal calf serum (16). Cell cultures for all  
experiments were initiated with cells in logarithmic  
growth phase (day 2 cultured cells) at a density of  $10^5$   
cells/ml. Inducer compounds were added in the final  
15 concentrations indicated below, dissolved in culture  
medium without fetal calf serum unless otherwise  
indicated. Cell density and benzidine reactivity were  
determined as described (16).

20 Commitment to terminal differentiation, characterized by  
limited cell division (colony size <32 cells) and  
accumulation of hemoglobin (benzidine reactive colonies)  
was assayed by a colony cloning assay using 2%  
methylcellulose as described (25) (see Table 1 for  
results).

25 HL-60 human leukemia cells, derived from peripheral blood  
leukocytes of a patient with acute promyelocytic leukemia  
(40). Induced differentiation of HL-60 cells assayed by  
determining the proportion of cells that developed the  
30 capacity to reduce nitroblue tetrazolium (NBT) (41) (see  
Table 2 for results).

- 35 -

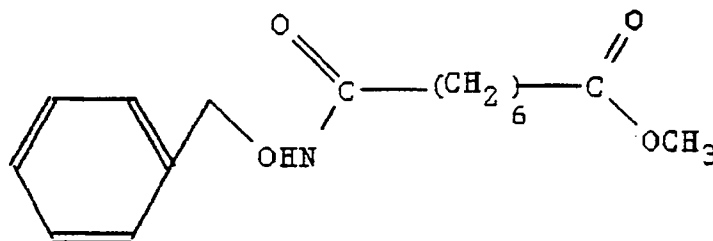
ChemistryThe compounds having the structure:Preparation of  $\text{PhCH}_2\text{ONHOC}(\text{CH}_2)_6\text{COOCH}_3$ :

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A solution of suberic acid monomethyl ester (1.9 g; 0.01 mol), oxaloyl chloride (1.75 mL; 2.54 g; 0.02 mol) and 0.1 mL DMF in benzene (200 mL) was stirred overnight at room temperature. The solvent was evaporated and oily residue was dissolved in chloroform (~20 mL) and mixed together with chloroform solution (100 mL) of O-benzylhydroxylamine (2.46 g; 0.02 mol) and pyridine (1.6 mL; 1.68 g; 0.02 mol). The reaction mixture was stirred at room temperature overnight. The chloroform solution was washed with water (50 mL), 10% hydrochloric acid, and again with water (2 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was slurried in hexanes (~100 mL) and filtered. The yield of  $\text{PhCH}_2\text{ONHOC}(\text{CH}_2)_6\text{COOCH}_3$  was 2.61 g (89%).

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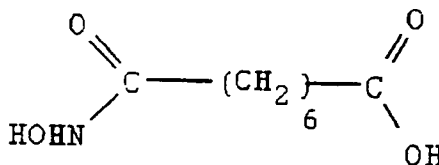
The above suberic acid monobenzyloxyamide monomethyl ester (1 g; 3.4 mol) was dissolved in dry methanol (50

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mL) and 5% Pd-C (50 mg) was added. The black suspension was shaken under hydrogen pressure (~50 psi) overnight at room temperature. The catalyst was separated by filtration, and filtrate was evaporated. The solid residue was slurried in hexanes (~20 mL) and filtered. The yield of the monomethyl ester monohydroxamic acid of suberic acid was 900 mg (95%).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 8.89 (s, broad, NHOH, 1H); 3.57 (s, CH<sub>3</sub>, 3H); 2.27 (t, J=7.4Hz, CH<sub>2</sub>COOCH<sub>3</sub>, 2H); 1.91 (t, J=7.4Hz, CH<sub>2</sub>CONHOH, 2H); 1.49 (m, 4H), 1.24(m, 4H).

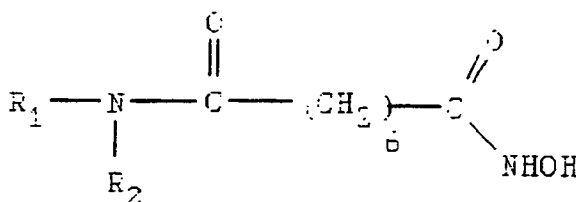
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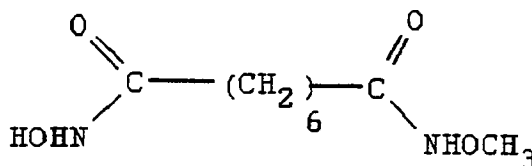
Suberic acid monobenzyloxyamide monomethyl ester (1g; 3.4 mmol) and potassium hydroxide (210 mg; 3.75 mmol) were dissolved in 10 mL of methanol-water (4:1) mixture. The reaction mixture was refluxed two hours and solvent was evaporated. The solid residue was dissolved in 5 mL water and acidified with conc. hydrochloric acid to pH~5. White precipitate was filtered, dried and crystallized from ethyl acetate-hexanes. The yield of suberic acid monobenzyloxyamide was 820 mg (86%). The product was dissolved in methanol (50 mL) and 5% Pd-C (50 mg) was added. The reaction mixture was shaken under hydrogen pressure (50 psi) overnight. The catalyst was separated by filtration and filtrate was evaporated. The solid residue was slurried in hexanes and filtered. The yield of suberic acid monohydroxamic acid was 520 mg (81%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 11.96 (s, broad, COOH, 1H); 10.31 (s, NHOH, 1H); 8.63 (s, broad, NHOH, 1H); 2.17 (s, J=7.4Hz, CH<sub>2</sub>COOH, 2H); 1.91 (s, CH<sub>2</sub>CONHOH, 2H); 1.46 (m,

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4H); 1.22 (m, 4H).

Compounds having the structure:General Procedure

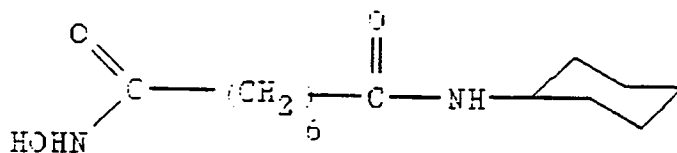
A pyridine (500 mL) solution of O-benzylhydroxylamine (2.46 g; 0.02 mol), the corresponding amine (0.02 mol) and suberoyl chloride was stirred at room temperature overnight. The solvent was evaporated and the semisolid residue was dissolved in 1000 mL chloroform-methanol (4:1); the resulting solution was washed with water (2 x 100 mL), 10% hydrochloric acid (3 x 100 mL), and again with water (2 x 100 mL). Organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was dissolved in methanol (100 mL) and 5% Pd-C was added. The black suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was separated by filtration, and the filtrate was evaporated. The target products were isolated by column chromatography on silica gel with ethyl acetate-tetrahydrofuran.

Yield 1.1 g (26%). <sup>1</sup>H NMR (DMSO-D<sub>6</sub>, 200 MHz), δ (ppm)

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10.93 (s,  $\text{NHOCH}_3$ , 1H); 10.32 (s,  $\text{NHOH}$ , 1H); 8.66 (s,  $\text{NHOH}$ , 1H); 3.55 (s,  $\text{CH}_3$ , 3H); 1.91 (t,  $J=7.6\text{Hz}$ ,  $\text{CH}_2\text{CO}-$ , 4H); 1.45 (m, 4H); 1.20 (m, 4H).

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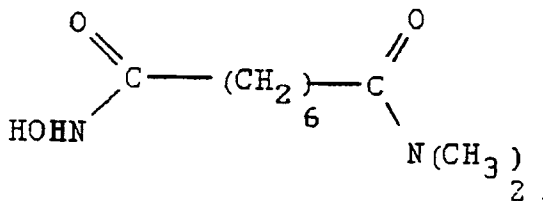


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Yield 1.2 g (21%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz),  $\delta$  (ppm) 10.31 (s,  $\text{NHOH}$ , 1H); 8.60 (s, broad,  $\text{NHOH}$ , 1H); 7.57 (d,  $J=7.6\text{Hz}$ ,  $\text{NH}-\text{C}_6\text{H}_{11}$ , 1H), 3.40 (m,  $\text{CH}-\text{NH}$ , 1H); 1.99 (t,  $J=7\text{Hz}$ ,  $\text{CH}_2\text{CONHC}_6\text{H}_{11}$ , 2H); 1.91 (t,  $J=7.6\text{Hz}$ ,  $\text{CH}_2\text{CONHOH}$ , 2H); 1.63 (m, 4H); 1.44 (m, 6H); 1.20 (m, 8H).

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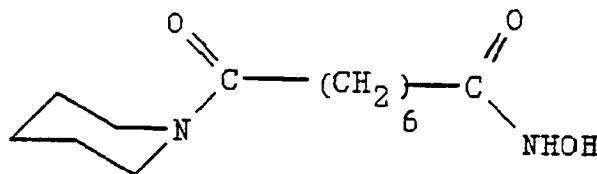
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Yield 870 mg (20%).  $^1\text{H}$  NMR ( $\text{DMSO}-D_6$ , 200 MHz),  $\delta$  (ppm) 10.31 (s,  $\text{NHOH}$ , 1H); 8.67 (s, broad,  $\text{NHOH}$ , 1H); 2.85 (d,  $J=30\text{Hz}$ ,  $\text{N}(\text{CH}_3)_2$ , 6H); 2.24 (t,  $J=7.4\text{Hz}$ ,  $\text{CH}_2\text{CON}(\text{CH}_3)_2$ , 2H); 1.91 (t,  $J=7.4\text{Hz}$ ,  $\text{CH}_2\text{COONHOH}$ , 2H); 1.50 (m, 4H); 1.20 (m, 4H).

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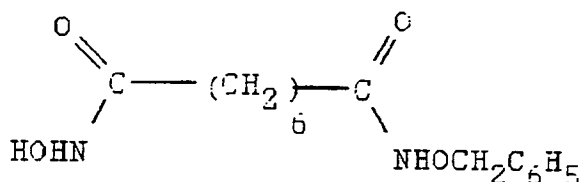
Yield 1.4 g (27%);  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz),  $\delta$  (ppm) 10.31 (s,  $\text{NHOH}$ , 1H); 8.67 (s,  $\text{NHOH}$ , 1H); 3.40 (2t,  $\text{CH}_2\text{N}$ , 4H); 2.20 (t,  $J=7.4\text{ Hz}$ ,  $\text{CH}_2\text{CON}(\text{CH}_2)_3$ , 2H); 1.91 (t,  $J=7.4\text{Hz}$ ,



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CH<sub>2</sub>CONHOH, 2H); 1.10-1.60 (m, broad, 14 H).

Compound having structure:

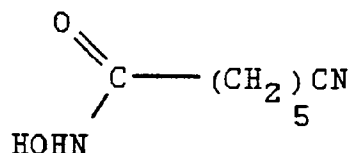


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The chloroform (500 mL) solution of O-benzylhydroxylamine (1.23 g; 0.01 mol), O-(trimethylsilyl)hydroxylamine (1.1 g; 0.01 mol), pyridine (1.6 mL; 1.7 g; 0.02 mol) and suberoyl chloride (1.8 mL; 2.11 g; 0.01 mol) was stirred at room temperature overnight. The reaction suspension was diluted with methanol (100 mL), washed with 10% hydrochloric acid (3 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was subjected to chromatography on silica gel in ethyl acetate-tetrahydrofuran (4:1). The yield was 500 mg (17%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ (ppm) 11.09 (s, NHOCH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 1H); 10.31 (s, NHOH, 1H); 8.67 (s, broad, NHOH, 1H); 7.36 (s, C<sub>6</sub>H<sub>5</sub>, 5H), 4.76 (s, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 2H); 1.92 (t, J=7.4Hz, CH<sub>2</sub>CO-, 4H); 1.45 (m, 4H); 1.20 (m, 4H).

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Compound having the structure:



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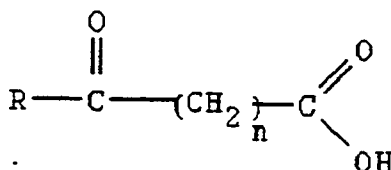
Into a cooled solution of potassium hydroxide (2.24 g; 0.04 mol) and O-benzylhydroxylamine hydrochloride in 30 mL of tetrahydrofuran-water (1:1) mixture, 6-bromohexanoyl chloride (3.1 mL; 4.27 g; 0.02 mol) was

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added. The reaction mixture was stirred at room temperature for one hour. The solvent was evaporated and solid residue was partitioned between chloroform (200 mL) and water (100 mL). Chloroform layer was washed with 10% hydrochloric acid (3 x 50 mL) and water (2 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The product was purified by crystallization from ethyl acetate-hexanes. The yield of N-benzyloxy-6-bromohexanoyl amide was 4.7 g (78%). A dimethylsulfoxide (250 mL) solution of N-benzyloxy-6-bromohexanoyl amide (4.5 g; 15 mmol) and sodium cyanide (7.35 g; 0.15 mol) was heated at 130°C overnight. The solvent was evaporated and solid residue was partitioned between chloroform (300 mL) and water (300 mL). The chloroform layer was washed with water (5 x 100 mL), dried over anhydrous magnesium sulfate, and evaporated. The oily residue was purified by column chromatography on silica gel in ethyl acetate-tetrahydrofuran (4:1) as an eluent. The yield of N-benzyloxy-6-cyanohehexanoylamide was 1.62 g (43%). The product was dissolved in methanol (50 mL) and 5% Pd-C (100 mg) was added. The black suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was isolated by filtration and filtrate was evaporated. The solid residue was slurried in hexanes (~20 mL) and filtered. The yield of N-hydroxy-6-cyanohehexanoylamide was 900 mg (overall yield 30%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.32 (s, NHOH, 1H); 8.65 (s, NHOH, 1H); 2.45 (t, J=7Hz, CH<sub>2</sub>CN, 2H) 1.93 (t, J=7Hz, CH<sub>2</sub>CONHOH, 2H); 1.49 (m, 4H); 1.33 (m, 2H).

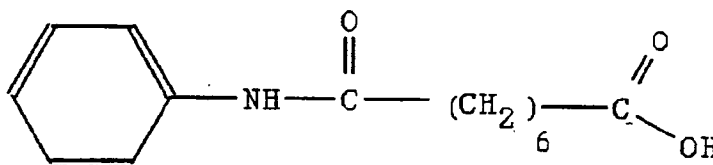
Compounds having the structure:



General Procedure

A diacid dichloride (0.01 mol) was added into a cooled (0°C) solution of potassium hydroxide (1.12 g; 0.02 mol) and corresponding amine (0.01 mol) in 30 mL of tetrahydrofuran-water (1:1) mixture. The reaction mixture was stirred at room temperature about one hour. Solvent was evaporated and the solid residue was partitioned between chloroform (300 mL) and water (300 mL). In some cases a small amount of methanol is necessary to dissolve all solid. The organic layer was washed with 10% potassium hydroxide (3 x 30 mL). The basic water extract was acidified with 10% hydrochloric acid. The precipitate was collected by filtration, dried and purified by crystallization from ethyl acetate or by column chromatography on silica gel in ethyl acetate-tetrahydrofuran (4:1). The yields are from 20-37%.

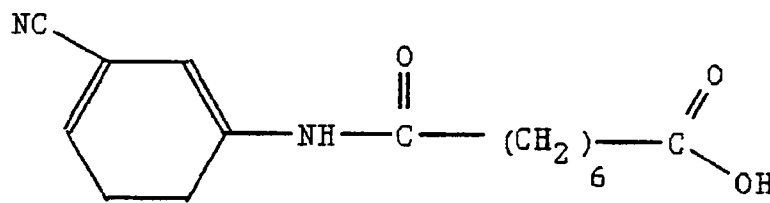
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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 11.97 (s, COOH, 1H); 9.84 (s, NH, 1H); 7.57 (d, J=7.4Hz, ortho aromatic protons, 2H); 7.26 (t, J=8.4Hz, meta aromatic protons, 2H); 6.99 (t, J=7.4Hz, para aromatic proton, 1H), 2.27 (t, J=7Hz, CH<sub>2</sub>CONHPh, 2H); 2.18 (t, J=7.2Hz, 2H); 1.52 (m, 4H); 1.28 (m, 4H).

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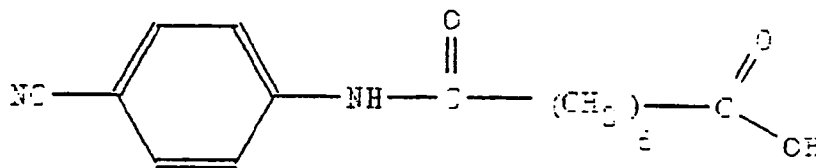
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 11.95 (s, COOH, 1H); 10.20 (s, NH, 1H); 8.10 (s, aromatic proton, 1H); 7.75

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(m, aromatic proton, 1H); 7.45 (m, aromatic proton, 2H); 2.28 (t, J=7.4Hz, CH<sub>2</sub>CONHAr, 2H); 2.21 (t, J=7.2Hz, CH<sub>2</sub>COOH, 2H); 1.46 (m, 4H); 1.20 (m, 4H).

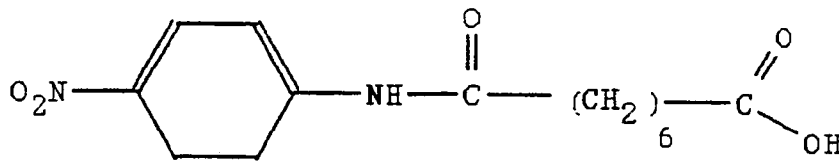
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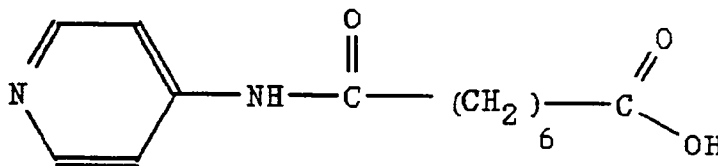
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 11.95 (s, COOH, 1H); 10.29 (s, NH, 1H); 7.75 (s, aromatic protons, 4H); 2.33 (t, J=7.2Hz, CH<sub>2</sub>CONHAr, 2H); 2.18 (t, J=7.4Hz, CH<sub>2</sub>COOH, 2H); 1.53 (m, 4H); 1.27 (m, 4H).

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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200MHz), 11.98 (s, broad, COOH, 1H); 10.48 (s, NH, 1H); 8.21 (d, J=9.2Hz, aromatic protons, 2H); 7.82 (d, J=9.2Hz, aromatic proton, 2H); 2.36 (t, J=7.4Hz, CH<sub>2</sub>CONHAr, 2H); 2.18 (t, J=7.2Hz, CH<sub>2</sub>COOH, 2H); 1.55 (m, 4H); 1.29 (m, 4H).

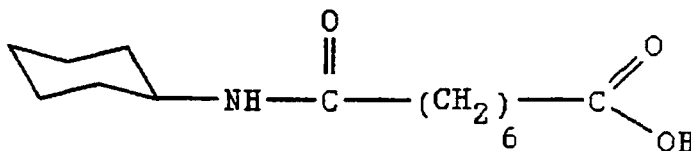
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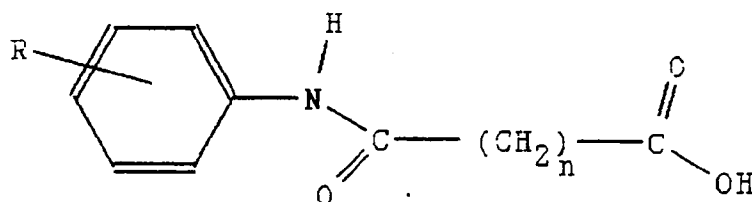
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 12.00 (s, broad COOH, 1H); 10.24 (s, NH, 1H); 8.38 (d, J=5.8Hz, aromatic protons, 2H); 7.55 (d, J=5.8Hz, aromatic protons, 2H); 2.33 (t, J=7.2Hz, CH<sub>2</sub>CONHAr, 2H); 2.18 (t, J=7.2Hz, CH<sub>2</sub>COOH, 2H); 1.52 (m, 4H); 1.27 (m, 4H).

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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200MHz), δ(ppm) 11.95 (s, COOH, 1H); 7.58 (d, J=8Hz); 3.50 (m, CH, 1H); 2.17 (t, J=7.2Hz, CH<sub>2</sub>COOH, 2H); 2.00 (t, J=7Hz, CH<sub>2</sub>CONH-, 2H); 1.60 (m, 4H); 1.46 (m, 6H); 1.20 (m, 8H). In the same way the following compounds were prepared and characterized:

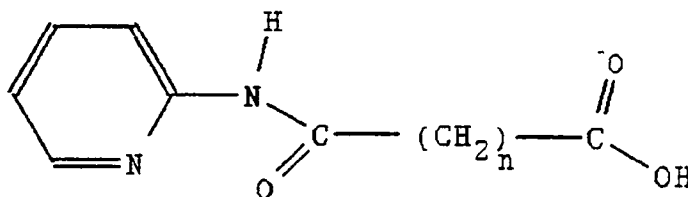
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wherein n = 4, 5, 6, 7, and 8; R is hydrogen; 2-, 3-, and 4-cyano; 2-, 3-, and 4-nitro; 2-, 3-, and 4-methylcyano; 2-, 3-, and 4-trifluoromethyl; 2-, 3-, and 4-fluoro;

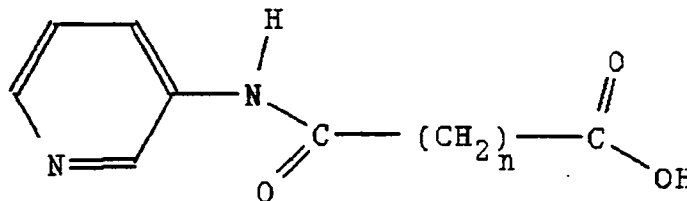
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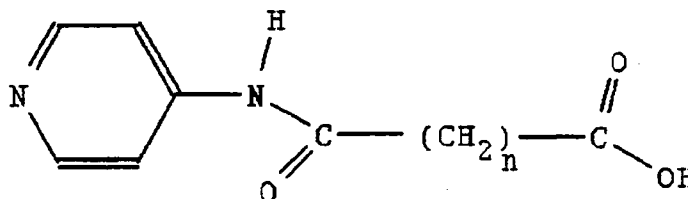
wherein n = 4, 5, 6, 7, and 8;

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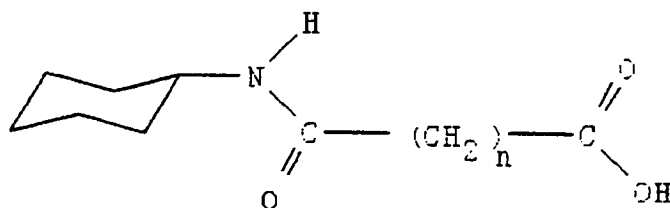
wherein n = 4, 5, 6, 7, and 8;



wherein  $n = 4, 5, 6, 7,$  and  $8;$

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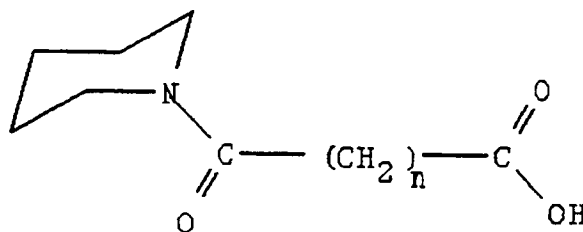
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wherein  $n = 4, 5, 6, 7,$  and  $8;$

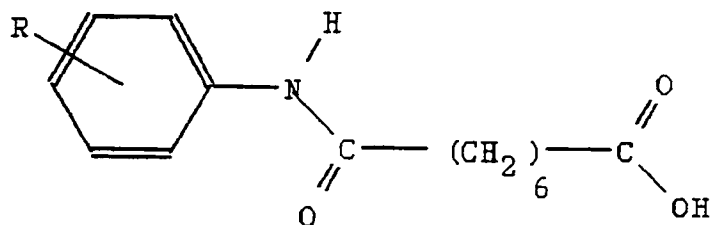
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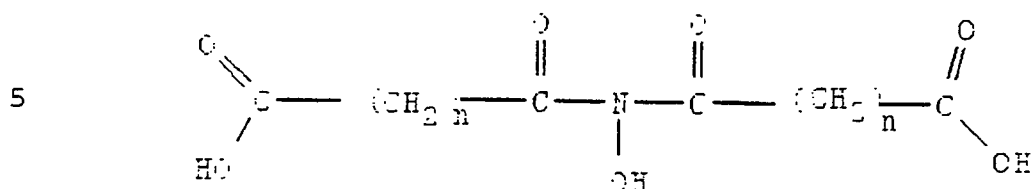
wherein  $n = 4, 5, 6, 7,$  and  $8;$

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30 wherein R is 2-, 3-, and 4-carboxy; 2-, 3-, and 4-aminocarbonyl; 2-, 3-, and 4-methylaminocarbonyl; 2-, 3-, and 4-dimethylaminocarbonyl; 2-, 3-, and 4-chloro; 2-, 3-, and 4-bromo; 2-, 3-, and 4-iodo; 2-, 3-, and 4-methyl; 2-, 3-, and 4-methoxy; 2-, 3-, and 4-hydroxy;  
35 2-, 3-, and 4-amino; and 2-, 3-, and 4-dimethylamino.

Compounds having the general structure:



wherein  $n = 4, 5, 6$ , and  $7$ .

### General Procedure A

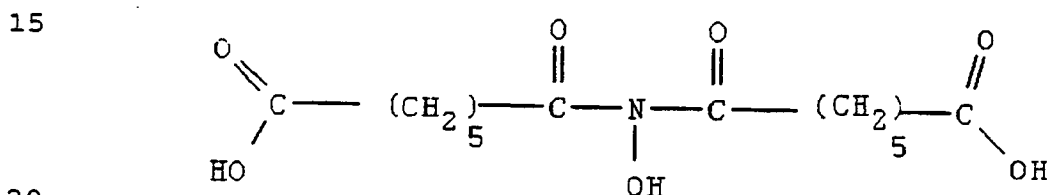
A pyridine (500 mL) suspension of O-benzylhydroxylamine hydrochloride (3.2 g; 0.02 mol) and the corresponding diacid dichloride (0.04 mol) was stirred at room temperature for three days. Water (10 mL) was added and stirring was continued overnight. The solvent was evaporated and solid residue was purified by column chromatography on silica gel in tetrahydrofuran-methanol. The diacid product was dissolved in methanol (100 mL) and 5% Pd-C (100 mg) was added. The reaction suspension was shaken overnight under hydrogen pressure (~50 psi). The catalyst was separated by filtration, solid residue was washed with hot methanol (5 x 50 ml). The combined methanolic filtrates were evaporated. The solid residue was slurried in acetone and filtered. The yield was 10-20%.

### General procedure B

30 A pyridine (500 ml) solution of O-benzylhydroxylamine  
(2.46 g; 0.02 mol) and the corresponding dicarboxylic  
acid monobenzyl ester monoacid chloride (0.04 mol) was  
stirred at room temperature overnight. The solvent was  
35 evaporated. The semisolid residue was dissolved in  
chloroform (300 mL) and extracted with 5% hydrochloric  
acid (2 x 50 mL), 10% potassium hydroxide (3 x 100 mL).

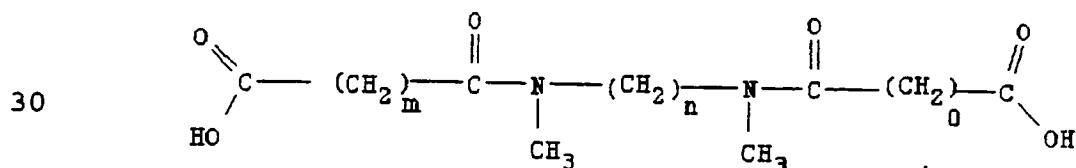
-46-

and water (2 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was purified by column chromatography on silica gel in ethyl acetate. The tribenzyl product was dissolved in methanol (100 mL) and 5% Pd-C (100 mg) was added. The reaction suspension was shaken under hydrogen pressure (~50 psi) at room temperature overnight. The solid was separated by filtration and washed with hot methanol (5 x 50 mL). The combined methanol filtrates were evaporated to solid residue. The solid residue was slurried in cooled acetone and filtered. The yield of target product was 30-60%.



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200MHz), δ(ppm) 11.53 (s, COOH, 1H); 2.41 (t, J=7.2Hz, CH<sub>2</sub>CON(OH)COCH<sub>2</sub>, 4H); 2.18 (t, J=7.0Hz, CH<sub>2</sub>COOH, 4H); 1.52 (m, 8H); 1.22 (m, H). MS (FAB, glycerin) 346(M + 1)

Compounds having the structure:

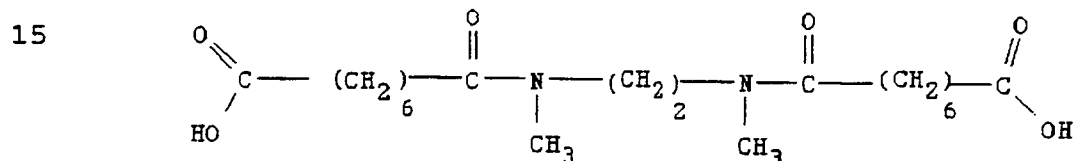


A pyridine (500 mL) solution of the monomethyl ester monoacid chloride of dicarboxylic acid (0.02 mol) and N,N'-dimethyl-1,ω-diaminoalkane (0.01 mol) was stirred at room temperature overnight. Solvent was evaporated and oily residue was dissolved in chloroform (300 mL). Chloroform solution was washed with water (3 x 50 mL),



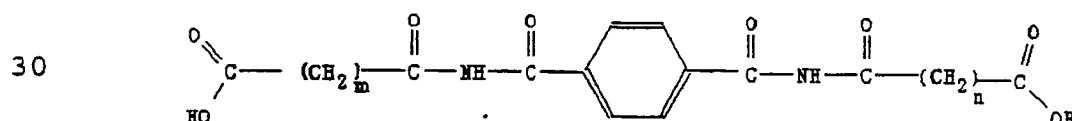
-47-

10% potassium hydroxide (3 x 50 mL), 10% hydrochloric acid (3 x 50 mL), and again with water (3 x 50 mL). The organic layer was dried and evaporated. The oily residue was dissolved in potassium hydroxide (1.2 g; 0.021 mol) in 80% methanol (100 mL). The reaction mixture was refluxed two hours. The solvent was evaporated and solid residue was dissolved in water (50 mL) and extracted with chloroform (3 x 50 mL). Water solution was acidified to pH~5 and concentrated (to volume of about 10 mL). The water solution or suspension was cooled down and precipitate was separated by filtration. The solid product was purified by crystallization from ethyl acetate. The yield was 40-60%.



20  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 200 MHz),  $\delta$ (ppm) 8.15 (s, broad,  $\text{COOH}$ , 2H); 3.52 + 3.45 (2s,  $\text{CH}_2\text{N}$ , 4H); 3.01 + 2.93 (2s,  $\text{CH}_3\text{N}$ , 6H); 2.30 (4t,  $\text{CH}_2\text{CO}$ , 8H); 1.60 (m, 8H); 1.32 (m, 8H).  
 $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz),  $\delta$ (ppm) 3.44 + 3.336 + 3.36 (3s,  $\text{CH}_2\text{N}$ , 4H); 2.94 + 2.90 + 2.79 (3s,  $\text{CH}_3\text{N}$ , 6H); 2.27 + 2.23 + 2.12 (3t,  $\text{CH}_2\text{CO}$ , 8H); 1.46 (m, 8H); 1.23 (m, 8H).

Compounds having the structure:

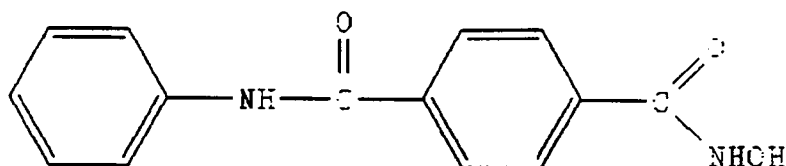


A pyridine (500 mL) solution of 6-aminocapric acid (2.6 g; 0.02 mol) and terephthaloyl chloride (2 g; 0.01 mol) was stirred at room temperature overnight (~12 hours), and at 90°C for 23 hours. The solvent was evaporated, and the solid residue was crystallized from water (10 mL) four times. The yield was 800 mg (19%).  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz),  $\delta$ (ppm) 12.8 (s, broad,  $\text{COOH}$ , 2H); 8.54 + 7.72

-48-

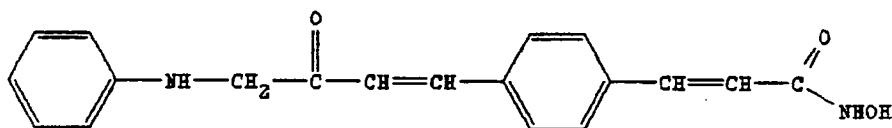
(2t, NH, 2H); 3.24 + 2.98 (2m, NHCH<sub>2</sub>, 4H); 2.20 + 2.03 (2m, CH<sub>2</sub>CO, 4H); 1.50 (m, 8H); 1.32 (m, 4H).

Compound having the structure:



Into a mixture of aniline (2.75 g; 0.03 mol), hydroxylamine hydrochloride (2.08 g; 0.03 mol), and potassium hydroxide (5.50g; 0.09 mol) in 50% tetrahydrofuran (100 mL) was slowly added at room temperature a tetrahydrofurane (20 mL) solution of terephthaloyl chloride (6 g; 0.03 mol). The reaction suspension was stirred at room temperature for thirty minutes. The solvent was evaporated. The solid residue was slurried in hot methanol (1000 mL) and dried over anhydrous magnesium sulfate. The methanol solution was separated by filtration and filtrate was evaporated. The solid residue was slurried in 20 mL cooled methanol and filtered. The white crystals were washed with ether (5 x 50 mL) and dried. The yield was 4.6 g (39%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 11.35 (s, broad, NHOH, 1H); 10.35 (s, NHPh, 1H); 9.19 (s, NHOH, 1H); 8.03 (d, J=8Hz, terephthalic protons, 2H); 7.89 (d, J=8Hz, terephthalic protons, 2H); 7.82 (d, J=7.4Hz, ortho anilide protons, 2H); 7.34 (t, J=7.4Hz, meta anilide protons, 2H); 7.10 (t, J=7.4Hz, para anilide proton, 1H).

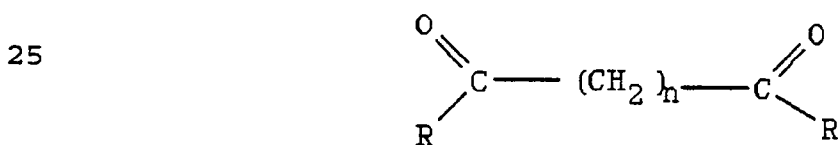
Compound having the structure:



-49-

A solution of 1,4-phenylenediacrylic acid (2.18 g; 0.01 mol) in thionyl chloride (50 mL; 81.55g; 0.68 mol) was refluxed overnight. The excess of thionyl chloride was evaporated. The solid was dissolved in tetrahydrofuran (20 mL), and added to a cooled (0°C) solution of potassium hydroxide (1.12 g; 0.02 mol) and aniline in 50% tetrahydrofuran. The reaction mixture was stirred at room temperature for thirty minutes. The solvent was evaporated. The solid residue was slurried in water and filtered. White crystals were dissolved in a small amount of methanol and purified on a silica gel column in tetrahydrofuran. The yield was 315 mg (10%). <sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.80 (s, NHOH, 1H); 10.23 (s, NHPh, 1H); 9.09 (s, NHOH, 1H); 7.69 (d, J=7.6Hz, ortho anilide protons, 2H); 7.64 (s, phenylene protons, 4H), 7.55 (d, J=15.8Hz, PhNHOCCH=CH-, 1H); 7.40 (d, J=15.8Hz, HONHOCCH=CH-, 1H); 7.33 (t, J=7.8Hz, meta anilide protons, 2H); 7.06 (t, J=7.2Hz, para anilide protons, 1H); 6.89 (d, J=15.8Hz, PhNHOCCH=CH-, 1H) 6.51 (d, J=15.8Hz, HONHOCCH=CH-, 1H).

Compounds having the structure:



wherein n = 4, 5, 6, 7, and 8.

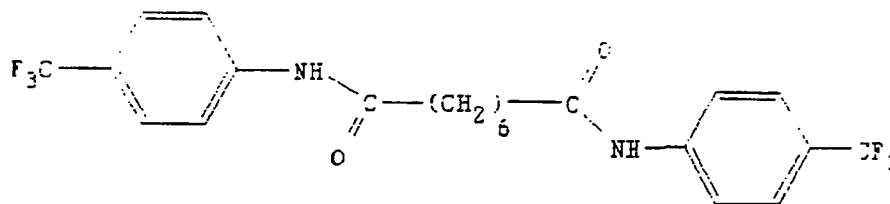
A chloroform solution of triethylamine (1.4 mL; 1.0 g; 0.01 mol), the corresponding amine (0.01 mol) and diacid dichloride (0.005 mol) was stirred at room temperature for five hours. If the reaction mixture was clear, it was washed with water (5 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated to a solid residue. If in the course of reaction a

- 50 -

precipitate was formed, the precipitate was separated by filtration. White crystals from filtration or solid residue from evaporation were crystallized from ethyl acetate, tetrahydrofuran, methanol, or their mixture.

5 The yields were from 60-90%.

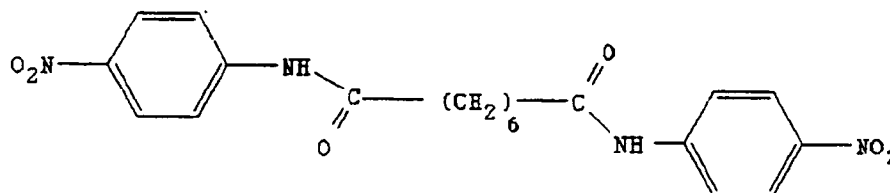
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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.23 (s, NH, 2H); 7.82 (d, J=9Hz, aromatic protons, 4H), 7.60 (d, J=9Hz, aromatic protons, 4H), 2.31 (t, J=7.4Hz, CH<sub>2</sub>CO, 4H); 2.61 (m, 4H); 1.32 (m, 4H).

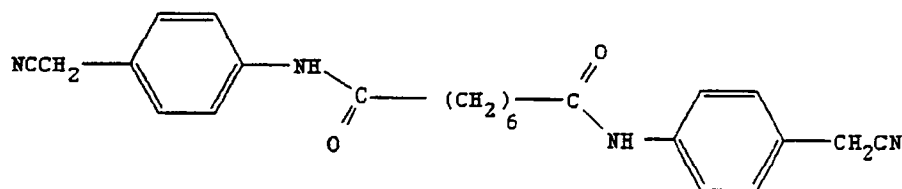
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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.48 (s, NH, 2H); 8.18 (d, J=9.2Hz, aromatic protons, 4H); 7.81 (d, J=9.2Hz, aromatic protons, 4H); 2.37 (t, J=7.2Hz, CH<sub>2</sub>CO-, 4H); 1.60 (m, 4H); 1.33 (m, 4H).

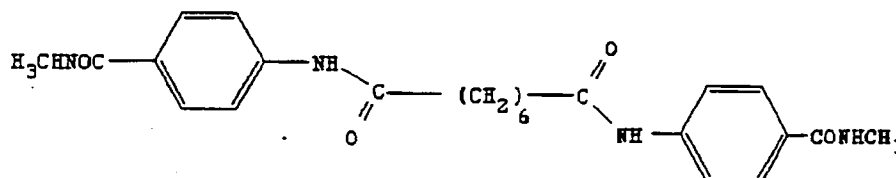
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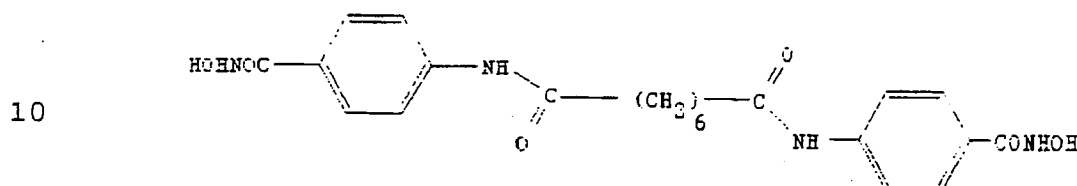
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 9.91 (s, NH, 2H), 7.58 (d, J=8.6Hz, aromatic protons, 4H); 7.26 (d, J=8.6 Hz, aromatic protons, 4H); 3.94 (s, CH<sub>2</sub>CN, 4H); 2.29 (t, J=7.4Hz, CH<sub>2</sub>CO-, 4H); 1.60 (m, 4H); 1.31 (m, 4H).

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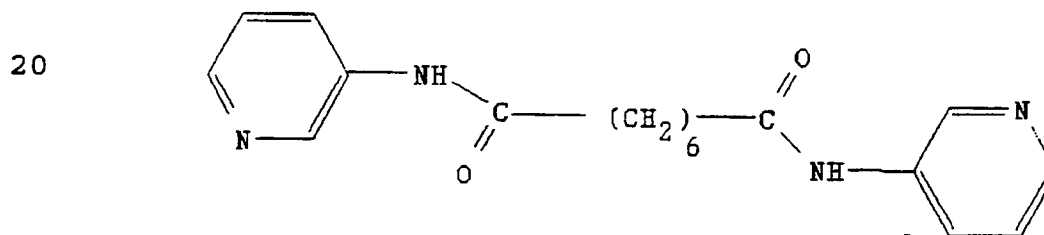


-51-

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.08 (s, CONHAr, 2H); 7.79 (d, J=8.6Hz, aromatic protons, 4H); 7.63 (d, J=8Hz, aromatic protons, 4H), 7.22 (s, H<sub>3</sub>CHNCO-, 2H); 3.32 (s, CH<sub>3</sub>, 6H); 2.31 (t, J=7Hz, CH<sub>2</sub>C-), 6H); 1.59 (m, 4H); 1.31 (m, 4H).

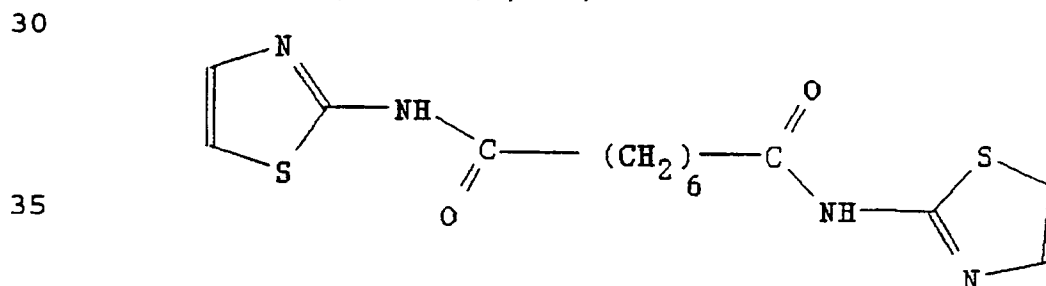


<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.90 (s, broad, NHOH, 2H); 10.05 (s, NHAr, 2H); 8.90 (s, broad, NHOH, 2H); 7.68 (d, J=9Hz, aromatic protons, 4H); 7.62 (d, J=9Hz, aromatic protons, 4H); 2.31 (t, J=7.2Hz, CH<sub>2</sub>CO-, 4H); 1.59 (m, 4H); 1.30 (m, 4H).



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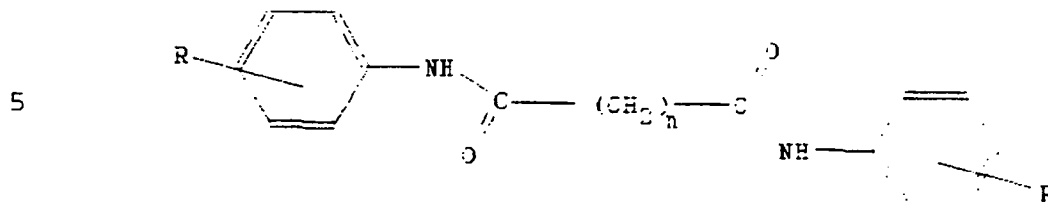
<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.06 (s, broad, NH, 2H); 8.71 (d, J=2.6Hz, aromatic protons, 2H); 7.31 (d + d, aromatic protons, 2H); 2.32 (t, J=7.4Hz, CH<sub>2</sub>CO-, 4H); 1.59 (m, 4H); 1.33 (m, 4H).



<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 12.00 (s, broad, NH, 2H); 7.43 (d, J=3.6Hz, aromatic protons, 2H); 7.16 (d, J=3.6Hz, aromatic protons, 2H); 2.41 (t, J=7.2Hz, CH<sub>2</sub>CONH-, 4H) 1.58 (m, 4H); 1.28 (m, 4H).

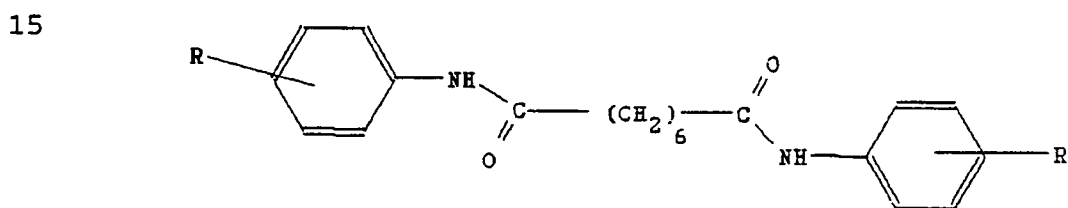
- 52 -

In the similar manner, the following compounds were prepared and characterized:

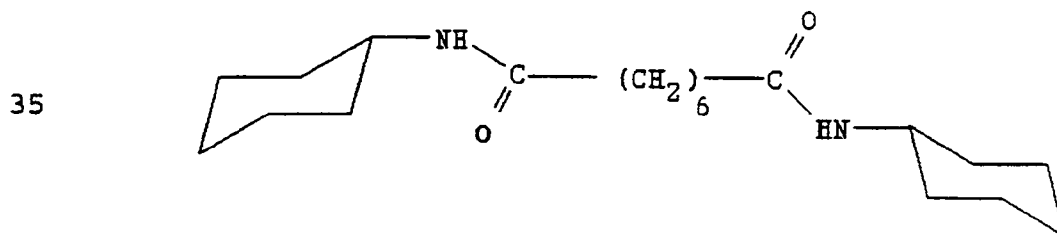
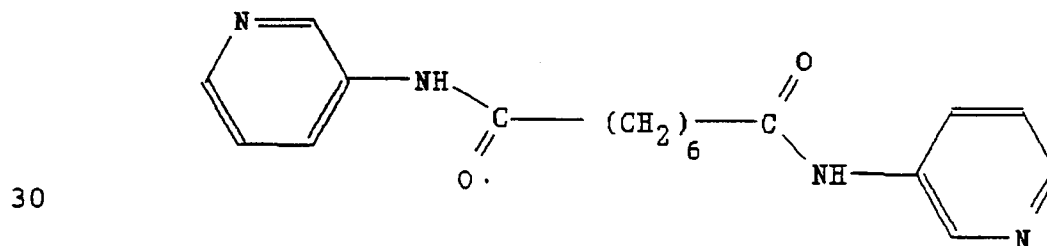


wherein  $n = 4, 5, 6, 7, \text{ and } 8$ ;

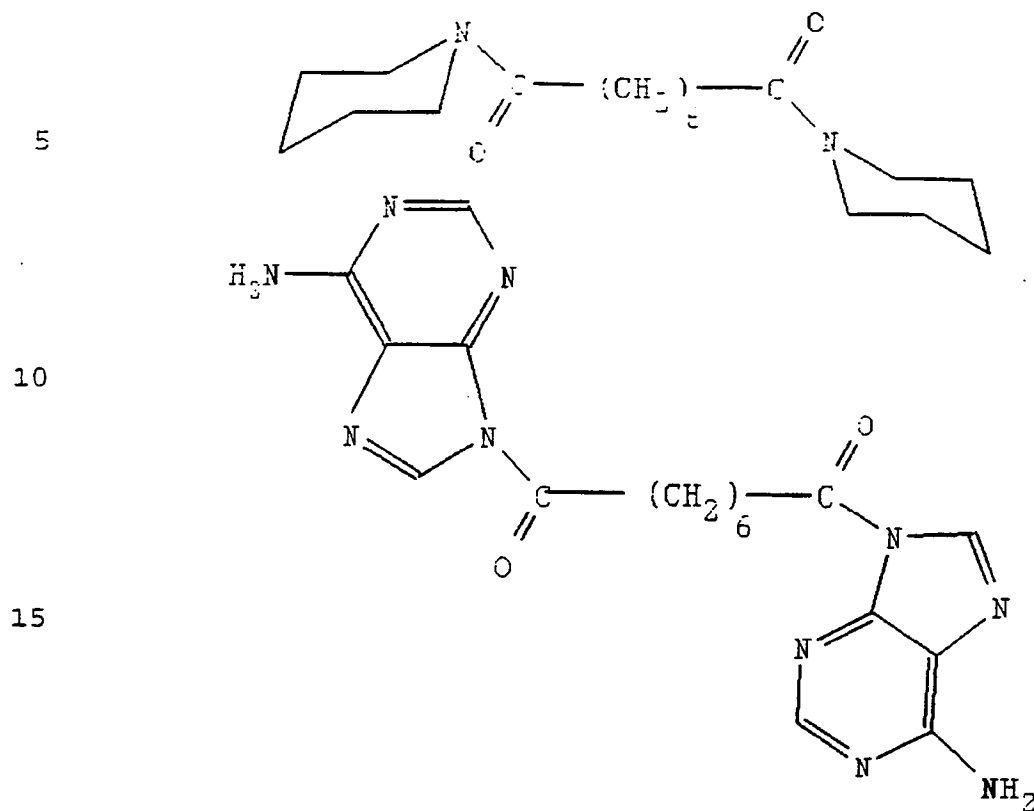
10 all compounds are symmetrical wherein R is 2-, 3-, and 4-cyano; 2-, 3-, and 4-methylcyano; 2-, 3-, and 4-nitro, 2-, 3-, and 4-carboxy; 2-, 3-, and 4-aminocarbonyl; 2-, 3- and 4-methylaminocarbonyl; 2-, 3-, and 4-dimethylaminocarbonyl; and 2-, 3-, and 4-trifluoromethyl;



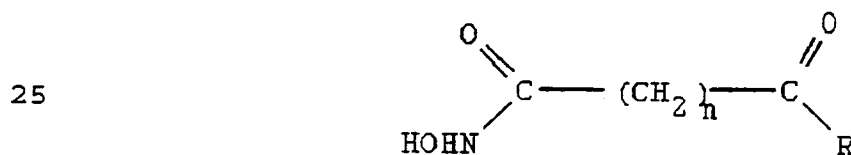
20 wherein R is 4-hydroxylaminocarbonyl; 4-methoxycarbonyl; 2-, 3-, and 4-chloro; 2-, 3-, and 4-fluoro; 2-, 3-, and 4-methyl; 2-, 3-, and 4-methoxy; 2,3-difluoro; 2,4-difluoro; 2,5-difluoro; 2,6-difluoro; 1,2,3-trifluoro, 3,4,5-trifluoro; 2,3,5,6-tetrafluoro; 25 2,3,4,5,6-pentafluoro.



- 53 -



Compounds having the structure:



wherein  $n = 4, 5, 6, 7, \text{ and } 8$ .

30

General procedure A

A diacid dichloride (0.01 mol) was added to a stirred solution of potassium hydroxide (1.68 g; 0.03 mol), hydroxylamine hydrochloride (0.7 g; 0.01 mol), and the corresponding aniline (0.01 mol) in 50% tetrahydrofuran (100 mL). The resulting reaction mixture was stirred at

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room temperature thirty minutes, and solvent was evaporated to solid residue. The solid residue was slurried in methanol (~100 mL) and dried over anhydrous magnesium sulfate. The methanol solution was separated  
5 by filtration and evaporated to a solid residue. The product was purified by column chromatography on silica gel in ethyl acetate-tetrahydrofuran (in most cases 3:1). The yields were 15-30%.

10 General procedure B

A solution of corresponding monomethyl ester of dicarboxylic acid (0.01 mol), oxaloyl chloride (0.03 mol), and a few drops DMF in benzene (500 mL) was stirred  
15 at room temperature overnight. The solvent was evaporated and the oily residue was dissolved in dry benzene (3 x 50 mL) and evaporated again. The tetrahydrofuran (50 mL) solution of monoester monoacid chloride of the corresponding dicarboxylic acid was  
20 slowly added to a cooled solution of the corresponding amine (0.01 mol) and pyridine (1.6 mL; 1.6 g; 0.02 mol) in tetrahydrofuran (200 mL). The reaction mixture was stirred at room temperature for an hour. The solvent was evaporated, the residue was dissolved in chloroform (300  
25 mL), and the chloroform solution was washed with 10% hydrochloric acid (3 x 50 mL), 10% potassium hydroxide (3 x 50 mL), and water (3 x 50 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated, yielding the pure monoester monoamide of dicarboxylic  
30 acid. The product was dissolved in 80% methanol with potassium hydroxide (0.56 g; 0.01 mol). The reaction mixture was refluxed two hours and evaporated to solid residue. The residue was dissolved in water (~20 mL) and acidified to ~pH 5 with 10% hydrochloric acid. The  
35 monoacid monoamide of the dicarboxylic acid was isolated by filtration of precipitate or extraction with water solution with chloroform. The isolated monoacid monoamide of the



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dicarboxylic acid was mixed together with an equivalent amount of O-benzylhydroxylamine and 1,3-dicyclohexylcarbodiimide in pyridine (~100 mL per 0.01 mol of O-benzylhydroxylamine) and was stirred at room temperature overnight. The solvent was evaporated and the solid residue was partitioned between chloroform (500 mL) and 10% hydrochloric acid (300 mL). The organic layer was washed with water (3 x 100 mL) and dried over anhydrous magnesium sulfate. The solvent was evaporated to solid residue. The solid residue was dissolved in large amounts of tetrahydrofuran and filtered through a short column of silica gel. The crude product was dissolved in methanol (100 mL) and 5% Pd-C was added. The reaction suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was separated by filtration and filtrate was evaporated to solid residue. The solid residue was slurried in hexanes and filtered. Mostly pure product was isolated in this way. If necessary further purification was achieved by column chromatography on silica gel with ethyl acetate-tetrahydrofuran. The yields were from 35% to 65%.

#### General procedure C

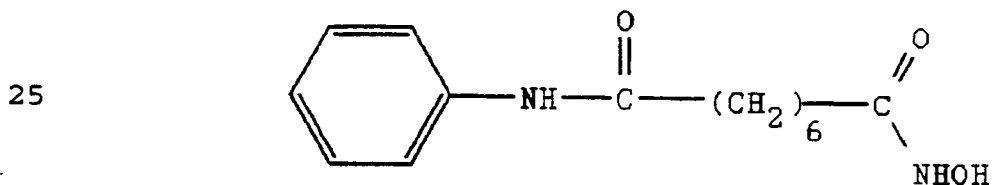
A pyridine (500 mL) solution of O-benzylhydroxylamine (1.23; 0.01 mol), the corresponding amine (0.01 mol), and the dichloride of the dicarboxylic acid (0.01 mol) was stirred at room temperature overnight. The solvent was evaporated and the white solid residue contains, judged by <sup>1</sup>H NMR, two symmetrical amides and a target unsymmetrical one. The solid residue was slurried in methanol and dried over anhydrous magnesium sulfate. The filtrate was evaporated and the solid residue was dissolved in methanol (~100 mL). Into the methanol solution 5% Pd-C (100 mg) was added and the black suspension was shaken under hydrogen pressure (~50 psi) overnight. The catalyst was separated by filtration and

-56-

the filtrate was evaporated. The product was isolated by column chromatography on silica with ethyl acetate-tetrahydrofuran. The yields were from 20% to 35%.

# 5 General procedure D

A chloroform solution of triethylamine (3 mL; 2.18 g; 0.0215 mol), the corresponding amine (0.01 mol), O-trimethylsilyl)hydroxylamine (1.05 g, 0.01 mol), and the corresponding diacid chloride of the dicarboxylic acid (0.01 mol) was stirred at room temperature overnight. The solvent was evaporated, the residue was dissolved in methanol (~10 mL), and into the methanol solution 10% ammonium chloride (~10 mL) was added. The resulting suspension was stirred at 50°C for two hours. The solvent was evaporated. The solid residue was slurried in methanol (300 mL) and dried over anhydrous magnesium sulfate. The methanol solution was separated by filtration and evaporated to a solid residue. The product was isolated by silica gel column chromatography with ethyl acetate-tetrahydrofuran. The yields were 20-33%.



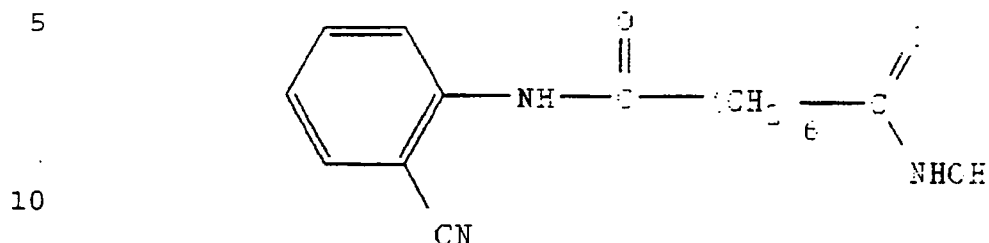
			C	H	N
30	Elemental analysis:	Calc.	63.62	7.63	10.60
		Found	63.58	7.59	10.48

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.31 (s, NHOH, 1H); 9.83 (s, NHPh, 1H); 8.64 (s, NHOH, 1H); 7.57 (d, J=8.2Hz, ortho aromatic protons, 2H); 7.26 (t, J=8.4Hz, meta aromatic protons, 2H), 6.99 (t, J=7.4Hz, para aromatic protons, 1H); 2.27 (t, J=7.4Hz, CH<sub>2</sub>CONHPh, 2H); 1.93 (t,

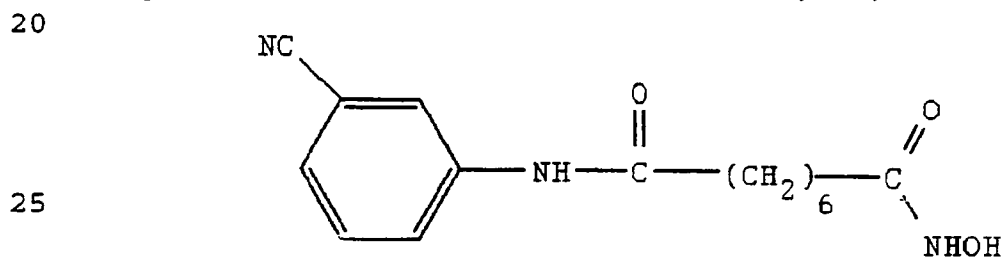
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- 57 -

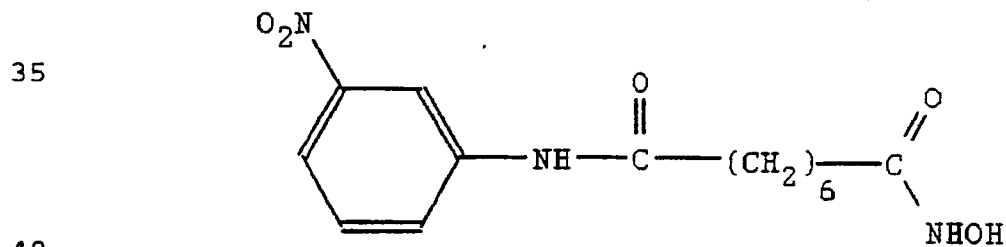
$J=7.2\text{Hz}$ ,  $\text{CH}_2\text{CONHOH}$ , 2H); 1.52 (m, 4H); 1.26 (m, 4H). MS (Fab, Glycerin) 172, 204, 232, 249, 265, (100%,  $M + 1$ ).



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz),  $\delta$ (ppm) 10.31 (s,  $\text{NHOH}$ , 1H); 10.08 (s,  $\text{NHPh}$ , 1H); 8.64 (s,  $\text{NHOH}$ , 1H); 7.78 (d,  $J=7.6\text{Hz}$ , aromatic protons, 1H); 7.66 (t,  $J=7.4\text{Hz}$ , aromatic protons, 1H); 7.48 (d,  $J=7.8\text{Hz}$ , aromatic protons, 1H); 7.29 (t,  $J=7.4\text{Hz}$ , aromatic protons, 1H); 2.34 (t,  $J=7\text{Hz}$ ,  $\text{CH}_2\text{CONHAr}$ , 2H); 1.93 (t,  $J=7.4\text{Hz}$ ,  $\text{CH}_2\text{CONHOH}$ , 2H); 1.58 (m, 4H); 1.27 (m, 4H).



$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz),  $\delta$ (ppm) 10.31 (s,  $\text{NHOH}$ , 1H); 10.21 (s,  $\text{NHPh}$ , 1H); 8.65 (s,  $\text{NHOH}$ , 1H); 8.09 (s, aromatic proton, 1H); 7.77 (m, aromatic proton, 1H); 7.49 (m, aromatic proton, 1H); 2.31 (t,  $J=7.2\text{Hz}$ ,  $\text{CH}_2\text{CONHAr}$ , 2H); 1.93 (t,  $J=7.2\text{Hz}$ ,  $\text{CH}_2\text{CONHOH}$ , 2H); 1.51 (m, 4H).

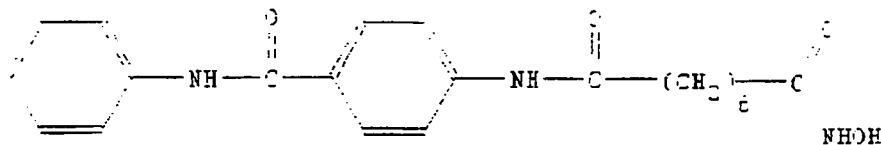


$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ , 200 MHz),  $\delta$ (ppm) 10.35 (s,  $\text{NHAr}$ , 1H); 10.31 (s,  $\text{NHOH}$ , 1H); 8.63 (s,  $\text{NHOH}$  + aromatic proton 2H); 7.88 (d,  $J=8\text{Hz}$ , aromatic protons, 2H); 7.57 (t,  $J=8\text{Hz}$ ,

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aromatic proton, 1H); 2.33 (t, J=7.6Hz, CH<sub>2</sub>CONHAr, 2H); 1.93 (t, J=7.4Hz, CH<sub>2</sub>CONHOH, 2H), 1.52 (m, 4H); 1.27 (m, 4H).

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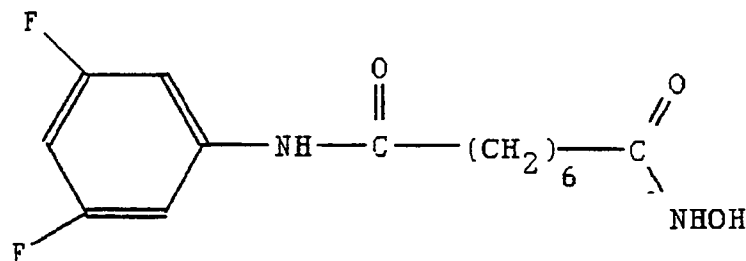


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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.33 (s, NHOH, 1H); 10.15 (s, NHAr, 1H); 10.09 (s, NHPh, 1H); 8.66 (s, NHOH, 1H); 7.91 (d, J=8.6Hz, aromatic protons, 2H); 7.76 (d, J=7.8Hz, ortho aniline protons, 2H); 7.71 (d, J=8.6Hz, aromatic protons, 2H); 7.33 (t, J=7.6Hz, meta anilide protons, 2H); 7.07 (t, J=7.4Hz, para anilide protons); 2.33 (t, J=7.5Hz, CH<sub>2</sub>NHAr, 2H); 1.93 (t, J=7.2Hz, CH<sub>2</sub>CNHH, 2H); 1.51 (m, 4H); 1.28 (m, 4H).

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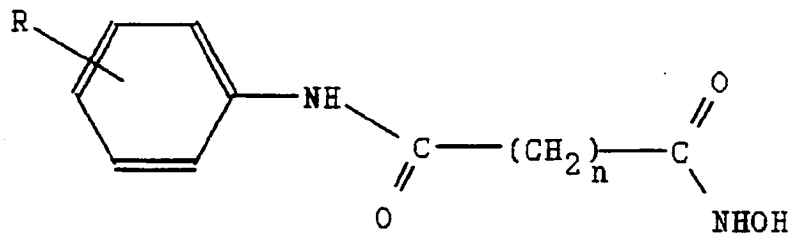
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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>, 200 MHz), δ(ppm) 10.32 (s, NHOH, 1H); 10.21 (s, NHAr, 1H); 8.65 (s, NHOH, 1H); 7.31 (d of d, J=10Hz(2.2Hz), aromatic protons, 2H); 6.84 (t of t, J=9.4Hz(2.4Hz), aromatic protons, 1H); 2.29 (t, CH<sub>2</sub>CONHAr, 2H); 1.93 (t, J=7.2Hz, CH<sub>2</sub>CONHOH, 2H); 1.51 (m, 4H); 1.26 (m, 4H).

35 In the same manner the following compounds were prepared and characterized:

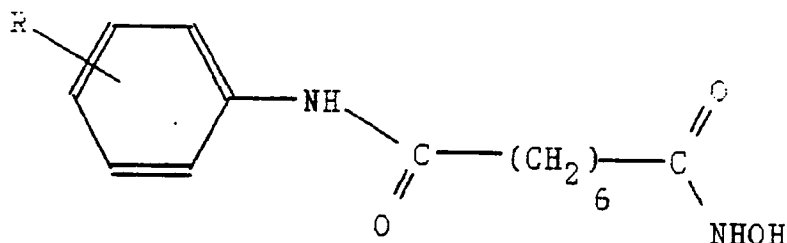
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-59-

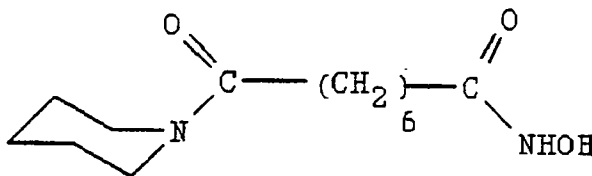
wherein n = 4, 5, 6, 7, and 8; and R is 2-, 3-, and 4-cyano; 2-, 3-, and 4-methylcyano; 2-, 3-, and 4-nitro; 2-, 3-, and 4-carboxy; 2-, 3-, and 4-aminocarbonyl; 2-, 3-, and 4-methylaminocarbonyl; 2-, 3-, and 4-dimethylaminocarbonyl; and 2-, 3-, and 4-trifluoromethyl;

10



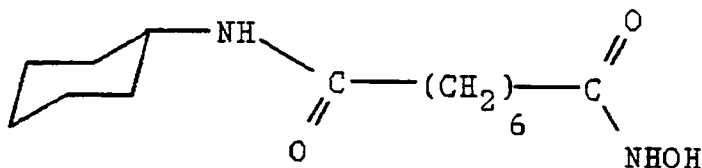
15 wherein R is 4-hydroxylaminocarbonyl; 4-methoxycarbonyl; 4-tetrazoyl; 2-, 3-, and 4-chloro; 2-, 3-, and 4-fluoro; 2-, 3-, and 4-methyl; 2-, 3-, and 4-methoxy; 2,3-difluoro; 2,4-difluoro; 2,5-difluoro; 2,6-difluoro; 1,2,3-trifluoro; 3,4,5-trifluoro; 2,4,5-trifluoro; 2,4,6-trifluoro; 2,3,6-trifluoro; 2,3,5,6-tetrafluoro; 2,3,4,5,6-pentafluoro; 2-, 3-, and 4-phenyl; 2-, 3-, and 4-benzyloxy; 4-hexyl; and 4-t-butyl;

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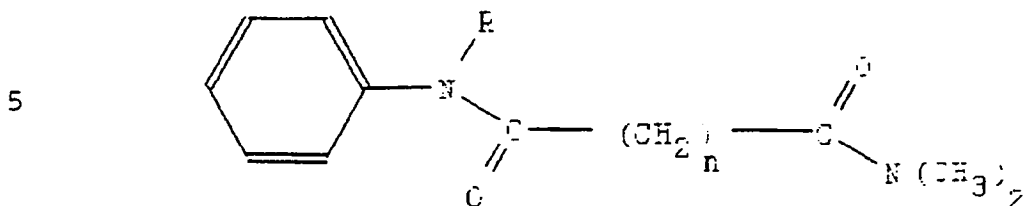
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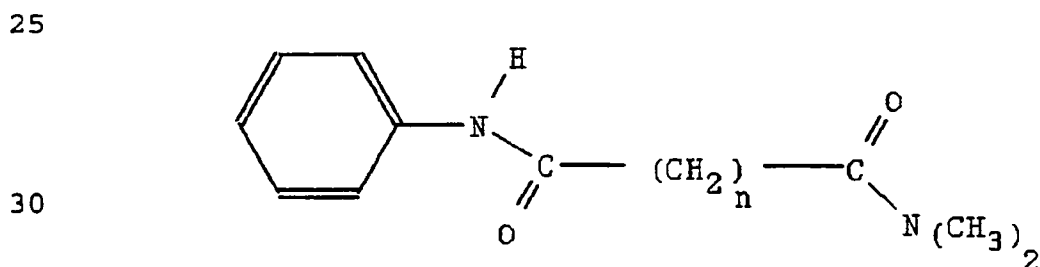
- 60 -

Compounds having the structure:



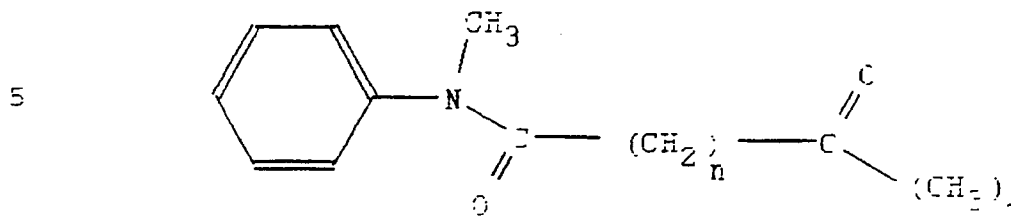
10 wherein  $n = 4, 5, 6, 7, \text{ and } 8$ ; and  $R$  is hydrogen or methyl.

A diacid dichloride (0.01 mol) was added into a stirred solution of potassium hydroxide (1.68 g; 0.03 mol), aniline or N-methylaniline (0.01 mol), and dimethylamine hydrochloride (0.805 g; 0.01 mol) in 50% tetrahydrofuran (100 mL). The reaction mixture was stirred thirty minutes at room temperature. The solvent was partitioned between chloroform (400 mL) and water (300 mL). The organic layer was washed with 10% hydrochloric acid (3 x 100 mL), 10% potassium hydroxide (3 x 100 mL), and water (2 x 100 mL). The organic layer was dried over anhydrous magnesium sulfate and evaporated. The solid residue was slurried in hexanes and filtered. The yield were 25-34%.



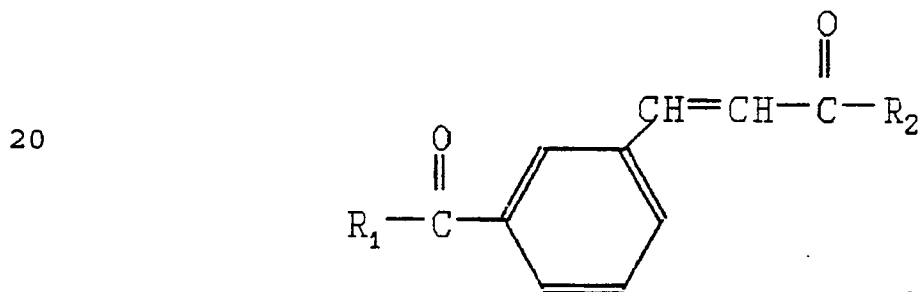
$^1\text{H}$  NMR (DMSO- $d_6$ , 200 MHz),  $\delta$ (ppm) 9.82 (s, NHPh, 1H); 7.58 (d,  $J=7.6\text{Hz}$ , ortho aromatic protons, 2H); 7.26 (t,  $J=7.4\text{Hz}$ , meta aromatic protons, 2H); 6.99 (t,  $J=7.4\text{Hz}$ , para aromatic proton, 1H); 2.85 (d,  $J=28\text{Hz}$ ,  $\text{N}(\text{CH}_3)_2$ , 6H); 2.28 (t,  $J=7.2\text{Hz}$ ,  $\text{CH}_2\text{CO}$ , 2H); 2.24 (t,  $J=7.4\text{Hz}$ ,  $\text{CH}_2\text{CO}$ , 2H); 1.51 (m, 4H); 1.29 (m, 4H).

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10  $^1\text{H}$  NMR (DMSO- $d_6$ , 200 MHz),  $\delta$  (ppm) 7.30 (m,  $\text{C}_6\text{H}_5$ , 5H); 3.13 (s,  $\text{H}_3\text{CNPh}$ , 3H); 2.83 (d,  $J=26\text{Hz}$ ,  $\text{N}(\text{CH}_3)_2$ , 6H); 2.17 (t,  $J=7.6\text{Hz}$ ,  $\text{CH}_2\text{CON}(\text{CH}_3)_2$ , 2H); 1.98 (t,  $J=7.4\text{Hz}$ ,  $\text{CH}_2\text{CON}(\text{CH}_3)\text{Ph}$ , 2H); 1.41 (m, 4H); 1.11 (m, 4H).

15 Compounds having the structure:



25 wherein  $\text{R}_1$ ,  $\text{R}_2$  are NHOH.

A solution of 18.4g (175 mmol) of  $\text{H}_2\text{N-OSiMe}_3$  in 100 ml abs.  $\text{CH}_2\text{Cl}_2$  was slowly added to a stirred solution of the corresponding diacid chloride of the dicarboxylic acid  
 30 (10g, 43.7 mmol) in 250 ml abs.  $\text{CH}_2\text{Cl}_2$ , which was kept at  $-78^\circ\text{C}$  under Argon. After the addition was complete, the mixture was allowed to warm to room temperature with stirring. A white precipitate formed during this process. After 2h at room temperature, the mixture was  
 35 heated to reflux for 30 min. to complete the substitution reaction. It was then again cooled at  $-78^\circ\text{C}$ , whereupon 10 ml of abs. MeOH were added with stirring. The cooling was then removed and the mixture was allowed to come to room temperature, during which period much more white

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precipitate appeared. After an additional 10 ml of MeOH had been added, the reaction was again heated to reflux for 30 min. The precipitate was filtered off and stirred with 100 ml of 0.2 N HCl for 2h. The product was then  
5 filtered, washed with water and dried in a vacuum (0.2 torr, room temperature) over  $\text{CaCl}_2$ . As the nmr spectrum (in  $\text{d}_6$ -DMSO) still indicated, the presence of water in the product after this process, the product was stirred with  
10 40 ml of dry acetone, filtered again and dried in the same fashion. The water peak in the nmr spectrum then decreased to the normal size expected for commercial  $\text{d}_6$ -DMSO. Yield: 8.8g (91%).

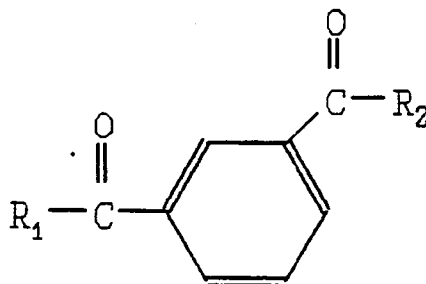
$^1\text{H}$ -NMR ( $\text{d}_6$ -DMSO, 200 MHz)  $\delta$ (ppm) 11.25 (br. s, 1H) and  
15 10.75 (br. s, 1H) (N-H); 9.1 (br. s, 2H, O-H); 7.9 (s, 1H,  $\text{C}_2$ -H); 7.7 (m, 2H,  $\text{C}_4$ -H,  $\text{C}_6$ -H); 7.5 (m, 2H,  $\text{C}_5$ -H, Ar-CH=CH-CONHOH); 6.5 (d,  $J=16$  Hz, 1H, Ar-CH= ).

MS (CI) :  $M+1$  223, 179, 161. Found: C, 54.96; calc.: C, 54.05%.

20

In a similar manner the known dicarboxylic acids corresponding to compounds having the following structures, wherein  $\text{R}_1$  and  $\text{R}_2$  are OH, were converted to their acid chlorides and then to the bis-hydroxamic acids  
25 and were also characterized by NMR and mass spectroscopy:

30



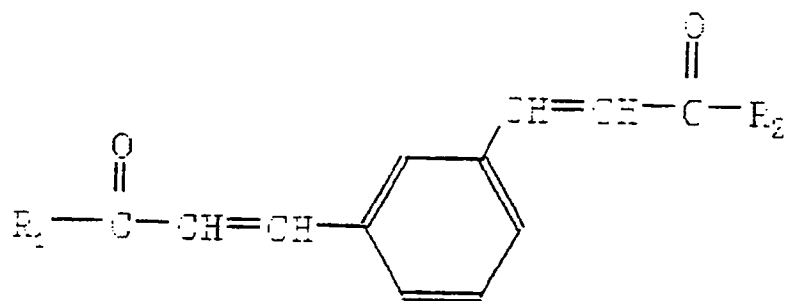
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and



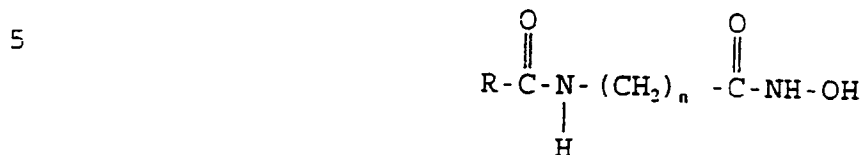
- 63 -

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Compounds having the structure:



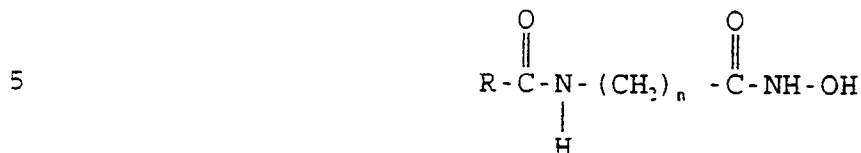
10    7-Benzoylamidoheptanoylhydroxamic acid, R = phenyl, n=6.

In a 25 mL flask, a solution of 0.571 g of 7-aminoheptanoic acid with 0.3145 g NaOH in 12 mL water was chilled to 0°C, and then 0.5 mL of benzoyl chloride in 8 mL dry THF was added dropwise over 30 minutes. After 3.5 hrs stirring the THF was evaporated and the solution was acidified to pH 1. The resulting precipitate of 7-benzoylaminoheptanoic acid was collected and washed with ether. It was characterized by NMR and mass spectroscopy (M+1=250). Then 0.20 g of this amide acid was treated for 3 hours with 0.1750 g of carbonyl diimidazole in 10 mL dry THF. To this stirring solution was added 0.1114 g of hydroxylamine hydrochloride, and the solution was stirred overnight at room temperature. Then 3 mL of 0.1 N HCl was added, the THF was evaporated, and the residue was taken up in 5 mL ethyl acetate and 3 mL brine. The produce amide hydroxamic acid was present as an ivory colored solid in the organic layer; it was collected by filtration in 60% yield. It was characterized by NMR and mass spectrum (M+1=265) and had m.p. = 105°C.

In a similar fashion analogs were prepared with n=5 or 6, and with R=p-cyanophenyl, m-cyanophenyl, and thiophenyl, by the use of the appropriate carboxylic acid chloride and 7-aminoheptanoic acid or 6-aminohexanoic acid in the first step.

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Compounds having the structure:



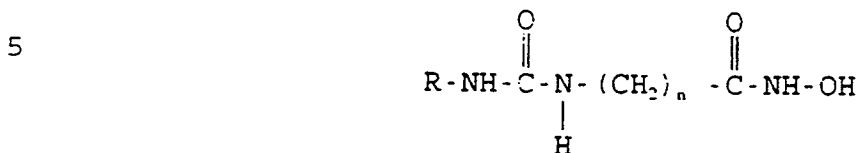
10 Suberoyl-(4-pyridyl)-amide hydroxamic acid, R = 4-pyridyl, n=6.

To an ice-cold solution of 6 mL suberoyl chloride in 20 mL THF was added 1.37 mL methanol and 4.7 mL triethylamine in 40 mL THF dropwise with stirring. After  
15 19 hours a solution of 3.2032 g 4-aminopyridine and 4.7 mL triethylamine in 250 mL THF was added dropwise with stirring and ice cooling. After 24 hours a small amount of white solid was removed by filtration, the THF was evaporated, and the crude product was chromatographed to  
20 afford 2.8879 g of the methyl ester of this amide ester was added to a solution of 0.9866 g hydroxylamine hydrochloride in 17 mL methanol with 0.8887 g NaOH, and the filtered solution was allowed to stand at room temperature for two days. The precipitated salt to the  
25 hydroxamic acid was washed with a little ethanol and stirred in 0.1242 g acetic acid in 10 mL water. After 48 hours 0.2291 g of the hydroxamic acid had crystallized, and it was collected and recrystallized from methanol to afford the pure product, m.p. 202-203°C. It was  
30 characterized by NMR and mass spectrum (M+1=266).

In a similar fashion the 2-pyridyl and 3-pyridyl analogs were prepared, using the appropriate amines.

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Compounds having the formula:



- 10 **m-Chlorophenylureido-6-hexanohydroxamic acid, R = m-chlorophenyl, n=5.**

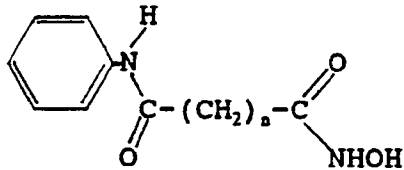
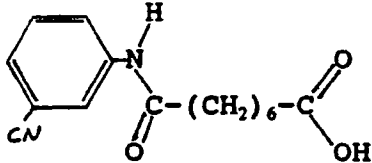
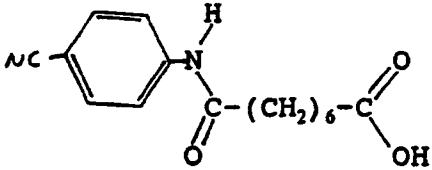
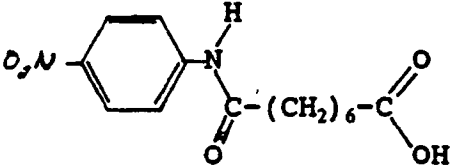
To 3.0 g of 6-aminocaproic acid in 150 mL THF was added 3.5 mL triethylamine, then 3 mL m-chlorophenyl isocyanate. After overnight standing the solution was filtered and concentrated by evaporation. Then partitioning between water and ether, followed by acidification of the aqueous layer to pH 3.0, afforded a precipitate of the ureidocarboxylic acid in 35% yield, characterized by NMR and mass spectrum (M+1=285). This was then converted to the hydroxamic acid product by treating 0.0418 g of the acid with 0.321 g carbonyl diimidazole in 25 mL THF. After 2 hours at room temperature, the solution was treated with 0.1948 g hydroxylamine hydrochloride and stirred for 20 hours. Then 15 mL 0.1 N HCl and 25 mL ethyl acetate were added and the THF was evaporated. The product appeared as crystals in the organic layer, and was collected in 38% yield. It had m.p. 162-163°C, and was characterized by NMR and elemental analysis: C, 51.62; H, 5.82; N, 13.47. Calc'd C, 52.0; H, 6.05; N, 14.00.

In a similar fashion the unsubstituted phenyl analog was prepared from phenyl isocyanate.

35

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TABLE 1

<u>CPD</u>	<u>Structure</u>	<u>Mol. Weight</u>	<u>Optimal Conc. (<math>\mu</math>M)</u>	<u>Benzidine Reactive Cells (%)</u>
	 $\text{C}_6\text{H}_5\text{NHC}(=\text{O})-(\text{CH}_2)_n-\text{C}(=\text{O})\text{NHOH}$			
1	n = 4 (known compound)	236	80	70
2	n = 5	250	20	84
3	n = 6	264	2.5	70
4	n = 7	278	20	8
5	n = 8	292	20	15
6	 $\text{p-CN-C}_6\text{H}_4\text{NHC}(=\text{O})-(\text{CH}_2)_6-\text{C}(=\text{O})\text{OH}$	274	31	44
7	 $\text{m-NC-C}_6\text{H}_4\text{NHC}(=\text{O})-(\text{CH}_2)_6-\text{C}(=\text{O})\text{OH}$	274	31	52
8	 $\text{p-O}_2\text{N-C}_6\text{H}_4\text{NHC}(=\text{O})-(\text{CH}_2)_6-\text{C}(=\text{O})\text{OH}$	294	12.5	32

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TABLE 1 (continued)

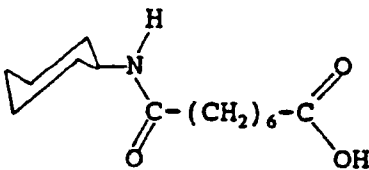
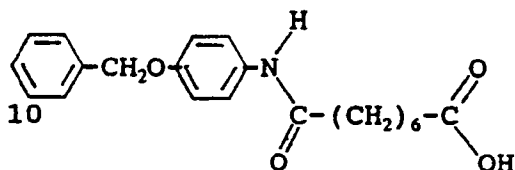
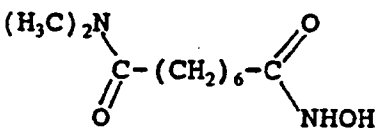
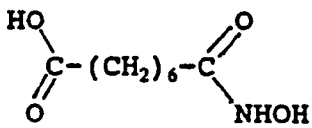
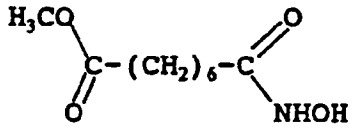
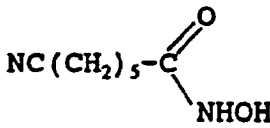
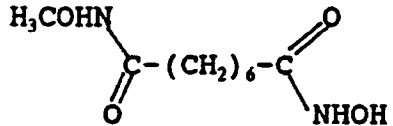
CPD	Structure	Mol. Weight	Optimal Conc. ( $\mu$ M)	Benzidine Reactive Cells (%)
9		225	50	20
10		355	250	26
11		216	60	53
12		189	250	35
13		203	60	17
14		156	125	30
15		218	20	43

TABLE 1 (continued)

CPD	Structure	Mol. Weight	Optimal Conc. ( $\mu$ M)	Benzidine Reactive Cells (%)
16		270	8	35
17		256	62	30
18		260	31	38
19		278	5	24
20		273	20	52
21		289	7	70
22		289	5	55
23		289	16	65
24		309	5	30

TABLE 1 (continued)

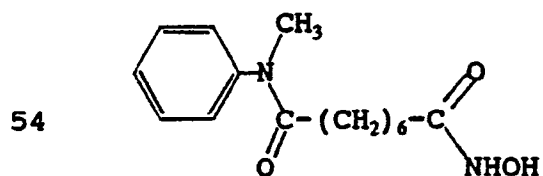
<u>CPD</u>	<u>Structure</u>	<u>Mol. Weight</u>	<u>Optimal Conc. (<math>\mu</math>M)</u>	<u>Benzidine Reactive Cells (%)</u>
25	R = 4-nitro	309	0.8	30
26	R = 3-trifluoromethyl	332	30	30
27	R = 4-trifluoromethyl	332	5	47
28	R = 2-amino	279	20	54
29	R = 4-cyanomethyl	303	1	30
30	R = 3-chloro	298.5	2	33
31	R = 4-azido ( $N_3$ )	304	2	47
32	R = 2-fluoro	282	4	65
33	R = 3-fluoro	282	1	25
34	R = 4-fluoro	282	4	43
35	R = 4-benzyloxy	370	4	20
36	R = 4-methoxycarbonyl	322	4	28
37	R = 4-methylaminocarbonyl	321	30	16
38	R = 2-bromo	343	8	45
39	R = 2-chloro	298.5	4	34
40	R = 4-bromo	343	1.6	47



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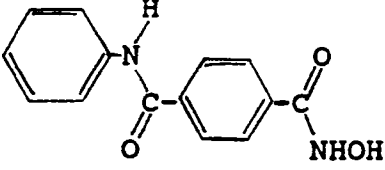
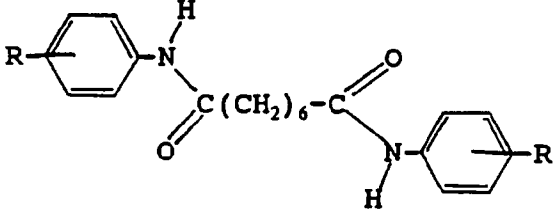
TABLE 1 (continued)

<u>CPD</u>	<u>Structure</u>	<u>Mol. Weight</u>	<u>Optimal Conc. (<math>\mu</math>M)</u>	<u>Benzidine Reactive Cells (%)</u>
41	R = 2,3-difluoro	300	8	24
42	R = 2,4,5-trifluoro	318	8	36
43	R = 2,3,6-trifluoro	318	31	53
44	R = 2,4,6-trifluoro	318	16	47
45	R = 2,4-difluoro	300	6	60
46	R = 2,3,4,5,6-pentafluoro	354	31	53
47	R = 3,4-difluoro	300	4	61
48	R = 3,4,5-trifluoro	318	8	55
49	R = 2,5-difluoro	300	4	70
50	R = 3,5-difluoro	300	2	73
51	R = 2-methoxy	294	8	36
52	R = 3-methoxy	294	6	38
53	R = 4-methoxy	294	6	37



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TABLE 1 (continued)

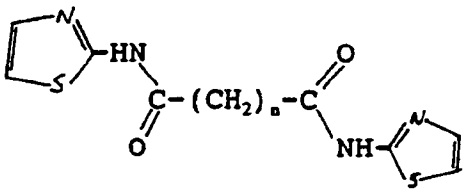
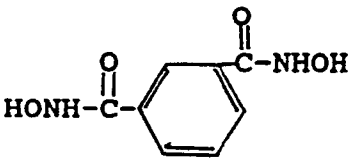
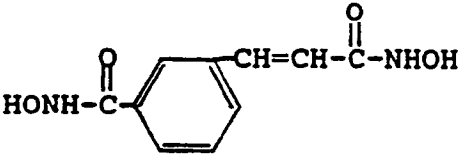
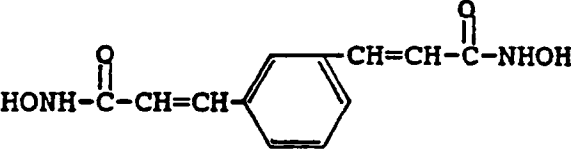
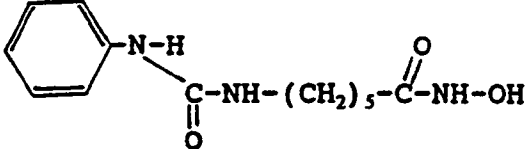
<u>CPD</u>	<u>Structure</u>	<u>Mol. Weight</u>	<u>Optimal Conc. (<math>\mu</math>M)</u>	<u>Benzidine Reactive Cells (%)</u>
55		256	30	53
				
56	R = 4-trifluoromethyl	460	50	20
57	R = 4(N)-hydroxylamino-carbonyl	442	8	10
58	R = 4-cyanomethyl	402	50	25
59	R = 2,4-difluoro	396	500	54
60	R = 2,6-difluoro	396	100	21
61	R = 3,5-difluoro	396	125	31
62	R = 2,3,6-trifluoro	432	250	28
63	R = 2,4,6-trifluoro	432	125	35
64	R = 2,3,4,5,6-pentafluoro	504	125	13
65	R = 4-nitro	414	25	14

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TABLE 1 (continued)

CPD	Structure	Mol. Weight	Optimal Conc. ( $\mu$ M)	Benzidine Reactive Cells (%)
66	$  \begin{array}{c}  \text{O} \quad \text{CH}_3 \quad \quad \text{CH}_3 \quad \text{O} \\  \parallel \quad   \quad \quad   \quad \parallel \\  (\text{H}_3\text{C})_2\text{N}-\text{C}-\text{CH}-(\text{CH}_2)_5-\text{CH}-\text{C}-\text{N}(\text{CH}_3)_2  \end{array}  $	270	1250	80
67	$  \begin{array}{c}  \text{O} \quad \text{CH}_3 \quad \quad \text{CH}_3 \quad \text{O} \\  \parallel \quad   \quad \quad   \quad \parallel \\  (\text{H}_3\text{C})_2\text{N}-\text{C}-\text{CH}-(\text{CH}_2)_4-\text{CH}-\text{C}-\text{N}(\text{CH}_3)_2  \end{array}  $	256	2500	90
68	$  \begin{array}{c}  \text{O} \quad \quad \text{CH}_3 \quad \quad \text{O} \\  \parallel \quad \quad   \quad \quad \parallel \\  \text{HOHN}-\text{C}-(\text{CH}_2)_2-\text{CH}-(\text{CH}_2)_2-\text{C}-\text{NHOH}  \end{array}  $	204	125	56
69	$  \begin{array}{c}  \text{O} \quad \quad \text{CONHOH} \quad \quad \text{O} \\  \parallel \quad \quad   \quad \quad \parallel \\  \text{HOHN}-\text{C}-(\text{CH}_2)_5-\text{CH}-(\text{CH}_2)_5-\text{C}-\text{NHOH}  \end{array}  $	333	60	40
70	$  \begin{array}{c}  \text{O} \quad \quad \text{F} \quad \quad \text{O} \\  \parallel \quad \quad   \quad \quad \parallel \\  \text{HOHN}-\text{C}-(\text{CH}_2)_2-\text{CH}-(\text{CH}_2)_2-\text{C}-\text{NHOH} \\  \quad \quad \quad   \\  \quad \quad \quad \text{F}  \end{array}  $	226	160	19

TABLE 1 (continued)

CPD	Structure	Mol. Weight	Optimal Conc. ( $\mu$ M)	Benzidine Reactive Cells (%)
				
71	n = 4	310	100	8
72	n = 5	324	250	10
73	n = 6	338	50	7
74	n = 7	352	100	10
75	n = 8	366	100	10
76		196	-	0
77		222	4	73
78		248	20	45
79		283.3	3	45

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TABLE 1 (continued)

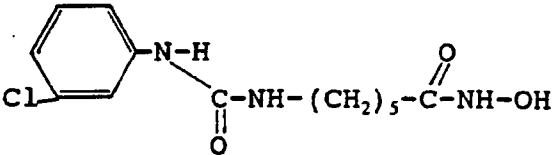
<u>CPD</u>	<u>Structure</u>	<u>Mol.</u> <u>Weight</u>	<u>Optimal</u> <u>Conc. (μM)</u>	<u>Benzidine</u> <u>Reactive</u> <u>Cells (%)</u>
80	 <chem>Clc1ccc(NC(=O)NCCCCC(=O)NO)cc1</chem>	284.74	3	32

TABLE 2

Induction of Differentiation of HL-60

<u>CPD</u>	<u>Mol. Weight</u>	<u>Optimal Conc. (<math>\mu</math>M)</u>	<u>NBT Positive (%)</u>
2	250	7	22
3	264	1	21
6	274	20	30
7	274	20	21
22	289	1.7	28
21	289	2	6
26	332	6	27
25	309	3	18
36	322	1	32
31	304	2.5	7
29	303	1	15
43	318	2	20
77	222	4	20
78	248	20	12

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TABLE 3

Induction of Differentiation of MELC

<u>CPD</u>	<u>Mol. Weight</u>	<u>Optimal Conc. (<math>\mu</math>M)</u>	<u>NBT Positive (%)</u>
3	264	3	65
77	222	4	61

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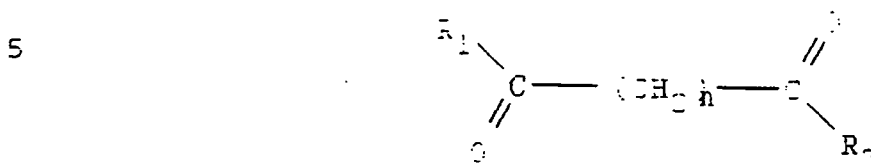
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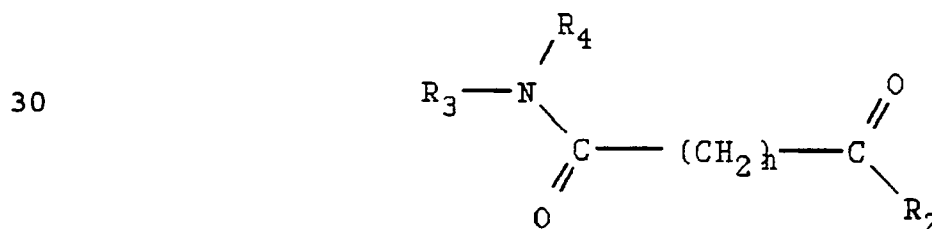
What is claimed is:

1. A compound having the structure:



10 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other; when  $R_1$  and  $R_2$  are the same, each is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiazoleamino group; when  $R_1$  and  $R_2$  are different,  $R_1 = R_3-N-R_4$ ,  
 15 wherein each of  $R_3$  and  $R_4$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl, alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy,  
 20 arylalkyloxy, or pyridine group, or  $R_3$  and  $R_4$  bond together to form a piperidine group and  $R_2$  is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and  $n$  is an integer from about 4 to about 8; or a pharmaceutically  
 25 acceptable salt thereof.

2. A compound of claim 1 having the structure:



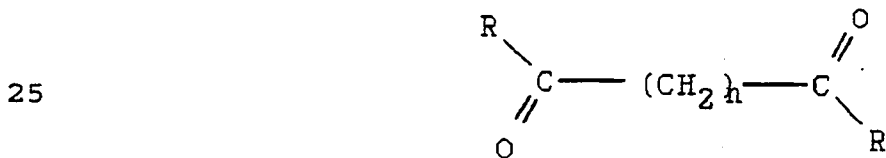
35 wherein each of  $R_3$  and  $R_4$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted, branched or unbranched alkyl,

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- alkenyl, cycloalkyl, aryl, alkyloxy, aryloxy, arylalkyloxy, or pyridine group, or  $R_3$  and  $R_4$  bond together to form a piperidine group;  $R_2$  is a hydroxylamino, hydroxyl, amino, alkylamino, dialkylamino or alkyloxy group; and  $n$  is an integer from about 4 to about 8.
- 5
3. A compound of claim 2, wherein  $R_2$  is a hydroxylamino, hydroxyl, amino, methylamino, dimethylamino, or methoxy group and  $n$  is 6.
- 10
4. A compound of claim 3, wherein  $R_4$  is a hydrogen atom and  $R_3$  is a substituted or unsubstituted phenyl group.
- 15
5. A compound of claim 4, wherein the phenyl group is substituted with a methyl, cyano, nitro, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.
- 20
- 25
- 30 6. A compound of claim 3, wherein  $R_4$  is a hydrogen atom and  $R_3$  is a cyclohexyl group.
- 35
7. A compound of claim 3, wherein  $R_4$  is a hydrogen atom and  $R_3$  is a methoxy group.
8. A compound of claim 3, wherein  $R_3$  and  $R_4$  bond together to form a piperidine group.

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9. A compound of claim 3, wherein  $R_1$  is a hydrogen atom and  $R_3$  is a hydroxyl group.
10. A compound of claim 3, wherein  $R_1$  is a hydrogen atom and  $R_3$  is a benzyloxy group.
11. A compound of claim 3, wherein  $R_1$  is a hydrogen atom and  $R_3$  is a  $\delta$ -pyridine group.
12. A compound of claim 3, wherein  $R_4$  is a hydrogen atom and  $R_3$  is a  $\beta$ -pyridine group.
13. A compound of claim 3, wherein  $R_4$  is a hydrogen atom and  $R_3$  is a  $\alpha$ -pyridine group.
14. A compound of claim 3, wherein  $R_3$  and  $R_4$  are both methyl groups.
15. A compound of claim 3, wherein  $R_4$  is a methyl group and  $R_3$  is a phenyl group.
16. A compound of claim 1 having the structure:



wherein R is a substituted or unsubstituted arylamino, cycloalkylamino, pyridineamino, piperidino, 9-purine-6-amine, or thiazoleamino group; and n is an integer from about 4 to about 8.

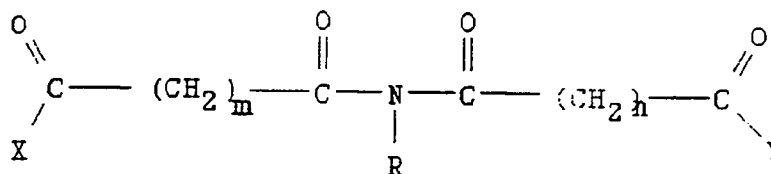
17. A compound of claim 16, wherein R is a substituted or unsubstituted phenylamino group.
18. A compound of claim 17, wherein the phenylamino

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group is substituted with a cyano, methylcyano, nitro, carboxyl, aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, trifluoromethyl, hydroxylaminocarbonyl, N-hydroxylaminocarbonyl, methoxycarbonyl, chloro, fluoro, methyl, methoxy, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 2,6-difluoro, 3,5-difluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 1,2,3-trifluoro, 3,4,5-trifluoro, 2,3,4,5-tetrafluoro, or 2,3,4,5,6-pentafluoro group.

19. A compound of claim 16, wherein R is a cyclohexylamino group.

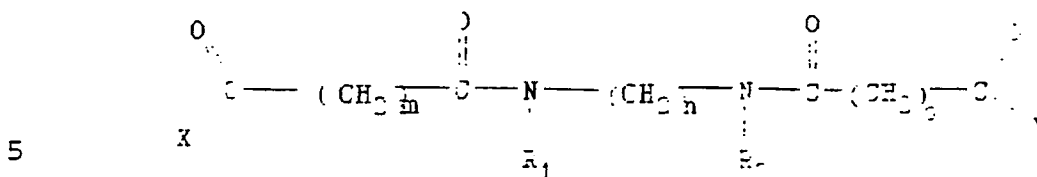
20. A compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; R is a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8; or a pharmaceutically acceptable salt thereof.

21. A compound of claim 20, wherein each of X, Y, and R is a hydroxyl group and each of m and n is 5.

22. A compound having the structure:

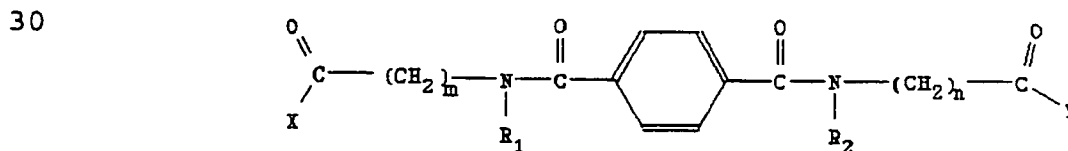


wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m, n, and o are independently the same as or different from each other and are each an integer from about 0 to about 8; or a pharmaceutically acceptable salt thereof.

23. A compound of claim 22, wherein each of X and Y is a hydroxyl group and each of R<sub>1</sub> and R<sub>2</sub> is a methyl group.

24. A compound of claim 23, wherein each of n and o is 6, and m is 2.

25. A compound having the structure:



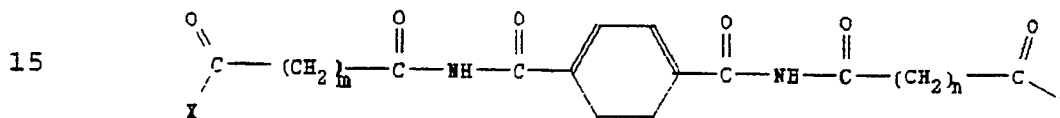
35 wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino,



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arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of  $m$  and  $n$  are independently the same as or different from each other and are each an integer from about 0 to about 8; or a pharmaceutically acceptable salt thereof.

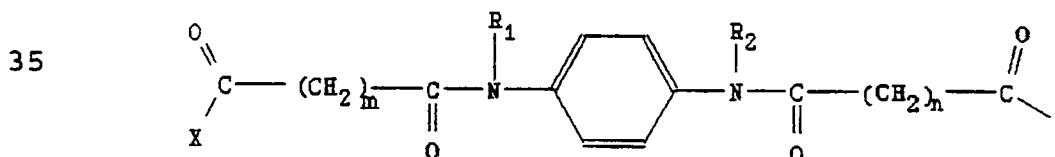
26. A compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylarylamino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and each of  $m$  and  $n$  are independently the same as or different from each other and are each an integer from about 0 to about 8; or a pharmaceutically acceptable salt thereof.

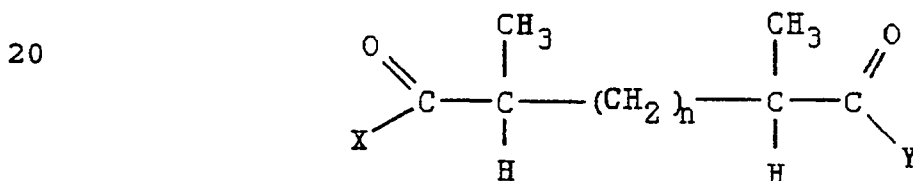
27. A compound of claim 26, wherein each of X and Y is a hydroxyl group and each of  $m$  and  $n$  is 5.

28. A compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; each of R<sub>1</sub> and R<sub>2</sub> are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, or aryloxy group; and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8; or a pharmaceutically acceptable salt thereof.

29. A compound having the structure:



wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; and n is an integer from about 0 to about 8; or a pharmaceutically acceptable salt thereof.

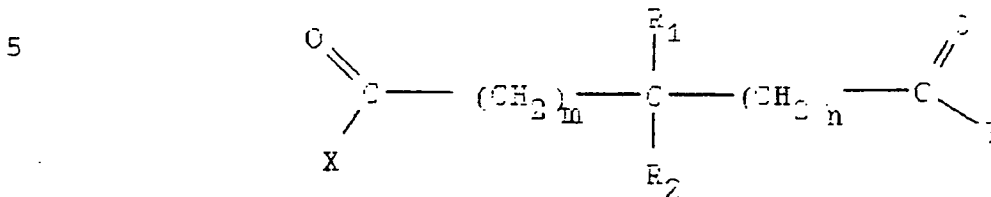
30. A compound of claim 29, wherein each of X and Y is a dimethylamino group and n is 5.

31. A compound of claim 29, wherein each of X and Y is

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a dimethylamino group and n is 4.

32. A compound having the structure:



10 wherein each of X and Y are independently the same as or different from each other and are a hydroxyl, amino or hydroxylamino group, a substituted or unsubstituted alkyloxy, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or

15 aryloxyalkylamino group; each of  $\text{R}_1$  and  $\text{R}_2$  are independently the same as or different from each other and are a hydrogen atom, a hydroxyl group, a substituted or unsubstituted alkyl, aryl, alkyloxy, aryloxy, carbonylhydroxylamino, or fluoro group;

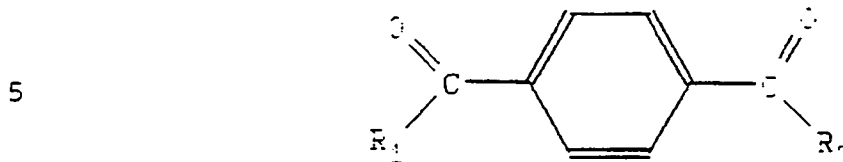
20 and each of m and n are independently the same as or different from each other and are each an integer from about 0 to about 8; or a pharmaceutically acceptable salt thereof.

25 33. A compound of claim 32, wherein each of X and Y is a hydroxylamino group;  $\text{R}_1$  is a methyl group;  $\text{R}_2$  is a hydrogen atom; and each of m and n is 2.

30 34. A compound of claim 32, wherein each of X and Y is a hydroxylamino group;  $\text{R}_1$  is a carbonylhydroxylamino group;  $\text{R}_2$  is a hydrogen atom; and each of m and n is 5.

35 35. A compound of claim 32, wherein each of X and Y is a hydroxylamino group; each of  $\text{R}_1$  and  $\text{R}_2$  is a fluoro group; and each of m and n is 2.

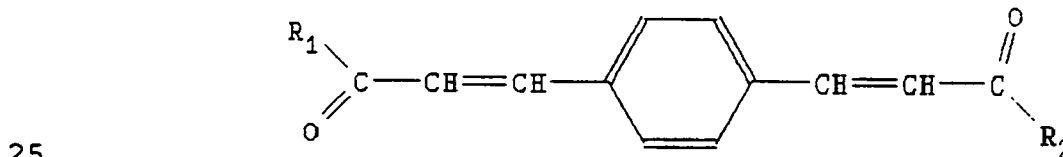
36. A compound having the structure:



- 10 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; or a pharmaceutically
- 15 acceptable salt thereof.

37. A compound of claim 36, wherein  $R_1$  is a phenylamino group and  $R_2$  is a hydroxylamino group.

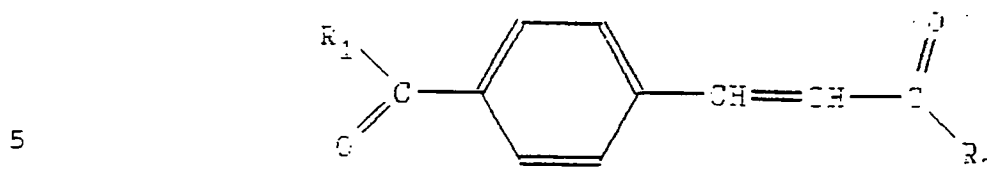
- 20 38. A compound having the structure:



- 30 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; or a pharmaceutically acceptable salt thereof.

- 35 39. A compound of claim 38, wherein  $R_1$  is phenylamino group and  $R_2$  is hydroxylamino group.

40. A compound having the structure:

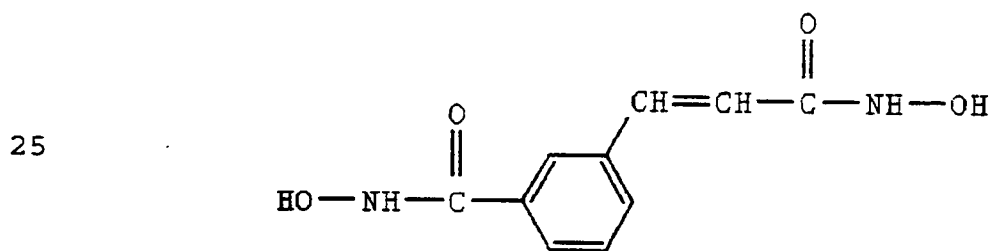


- 10 wherein each of  $R_1$  and  $R_2$  are independently the same as or different from each other and are a hydroxyl, alkyloxy, amino, hydroxylamino, alkylamino, dialkylamino, arylamino, alkylaryl amino, alkyloxyamino, aryloxyamino, alkyloxyalkylamino, or aryloxyalkylamino group; or a pharmaceutically acceptable salt thereof.

- 15 41. A compound of claim 40, wherein  $R_1$  is a hydroxylamino group.

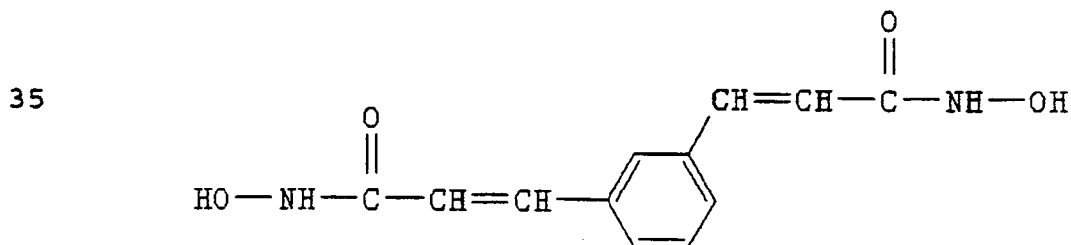
- 20 42. A compound of claim 40, wherein  $R_2$  is a hydroxylamino group.

43. A compound having the structure:



- 30 or a pharmaceutically acceptable salt thereof.

44. A compound having the structure:



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or a pharmaceutically acceptable salt thereof.

45. A compound having the structure:



wherein R is a substituted or unsubstituted phenyl, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

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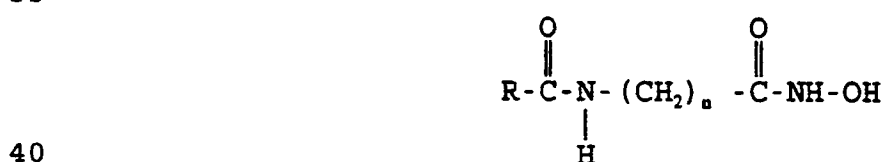
46. The compound of claim 45, wherein R is a substituted phenyl group.

20 47. The compound of claim 46, wherein the phenyl group is substituted with a methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminoxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

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48. A compound having the structure:

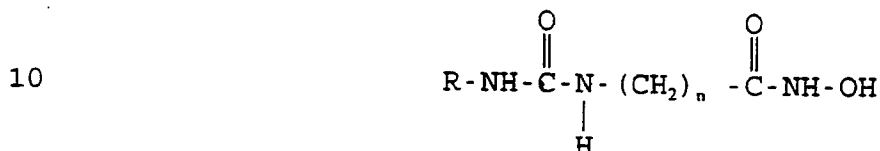


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wherein R is a substituted or unsubstituted 2-pyridine, 3-pyridine, or 4-pyridine and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

5

49. A compound having the structure:



15

wherein R is a substituted or unsubstituted phenyl, pyridine, piperidine or thiazole group and n is an integer from about 4 to about 8 or a pharmaceutically acceptable salt thereof.

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50. The compound of claim 49, wherein R is a substituted phenyl group.

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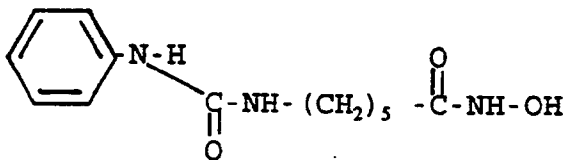
51. The compound of claim 50, wherein the phenyl group is substituted with a methyl, cyano, nitro, thio, trifluoromethyl, amino, aminocarbonyl, methylcyano, chloro, fluoro, bromo, iodo, 2,3-difluoro, 2,4-difluoro, 2,5-difluoro, 3,4-difluoro, 3,5-difluoro, 2,6-difluoro, 1,2,3-trifluoro, 2,3,6-trifluoro, 2,4,6-trifluoro, 3,4,5-trifluoro, 2,3,5,6-tetrafluoro, 2,3,4,5,6-pentafluoro, azido, hexyl, t-butyl, phenyl, carboxyl, hydroxyl, methoxy, phenyloxy, benzyloxy, phenylaminooxy, phenylaminocarbonyl, methoxycarbonyl, methylaminocarbonyl, dimethylamino, dimethylaminocarbonyl, or hydroxylaminocarbonyl group.

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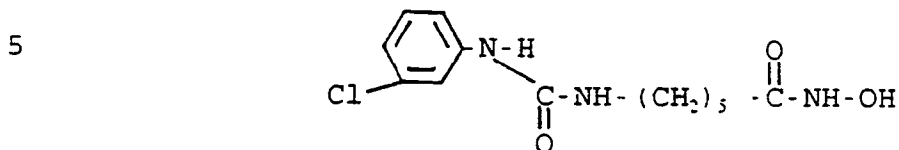
52. The compound of claim 49 having the structure:

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or a pharmaceutically acceptable salt thereof.

53. The compound of claim 51 having the structure:



or a pharmaceutically acceptable salt thereof.

10 54. A method of selectively inducing terminal  
differentiation of neoplastic cells and thereby  
inhibiting proliferation of such cells which  
comprises contacting the cells under suitable  
conditions with an effective amount of the compound  
15 of claim 1, 2, 16, 20, 22, 25, 26, 28, 29, 32, 36,  
38, 40, 43, 44, 47, 48, 51, or 52 or a  
pharmaceutically acceptable salt thereof, effective  
to selectively induce terminal differentiation.

20 55. A method of treating a patient having a tumor  
characterized by proliferation of neoplastic cells  
which comprises administering to the patient an  
effective amount of the compound of claim 1, 2, 16,  
20, 22, 25, 26, 28, 29, 32, 36, 38, 40, 43, 44, 47,  
25 48, 51, or 52 or a pharmaceutically acceptable salt  
thereof, effective to selectively induce terminal  
differentiation of such neoplastic cells and thereby  
inhibit their proliferation.

30 56. A pharmaceutical composition comprising a  
pharmaceutically acceptable carrier and a  
therapeutically effective amount of the compound of  
claim 1, 2, 16, 20, 22, 25, 26, 28, 29, 32, 36, 38,  
40, 43, 44, 47, 48, 51, or 52 or a pharmaceutically  
35 acceptable salt thereof.



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57. The pharmaceutical composition of claim 56, wherein the effective amount is an amount effective to selectively induce terminal differentiation of suitable neoplastic cells and less than an amount which causes toxicity in a patient.
58. The pharmaceutical composition of claim 56 in combination with an antitumor agent.
- 10 59. The pharmaceutical composition of claim 56 in sustained release form.
60. The pharmaceutical composition of claim 58 in sustained release form.

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/US95/06554

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(6) : Please See Extra Sheet.

US CL : Please See Extra Sheet.

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/532, 544, 551, 563, 615, 616; 560/18, 115, 159, 160; 562/450, 555; 564/156, 157, 158

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US, A, 2,279,560 (DIETRICH) 14 APRIL 1942, right column, page 1, lines 44+, and page 2, left column, lines 28+, particularly line 37.	1-60
Y	US, A, 2,279,973 (DIETRICH) 14 APRIL 1942, page 2, left column, lines 40-45, and right column, lines 1-31.	1-60



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:		*T	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
*A*	document defining the general state of the art which is not considered to be of particular relevance	*X*	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
*E*	earlier document published on or after the international filing date	*Y*	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
*L*	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*Z*	document member of the same patent family
*O*	document referring to an oral disclosure, use, exhibition or other means		
*P*	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search

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# INTERNATIONAL SEARCH REPORT

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## A. CLASSIFICATION OF SUBJECT MATTER:

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